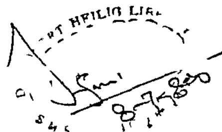
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A K. K. K. LUNDSGAARD EDI COEPTA



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Instructions to Contributors

Manuscripts from Scandinavian countries should be sent to the Chief Editor

From other countries to an International Editor

Acta Ophthalmologica publishes articles dealing with clinical and basic ophthalmology. Priority is to manuscripts which are original, brief and precise. Papers are accepted on the condition they have not and will not be published elsewhere, except under certain circumstances as when a paper has been read before a society. The author must then indicate the name of the society and date of the meeting. It is assumed that the author has considered the ethical aspects of his research and in this connection paid attention to the guidelines of the Helsinki declaration as revised in 1975. Articles, including references, must not exceed 10 printed pages. One printed Acta page contains about 3100 letters, space between words included. Additional pages, when accepted, must be paid for by the author at a rate of D.kr. 250 per page.

MANUSCRIPTS must be submitted in duplicate to facilitate rapid refereeing. They should be typewritten on one side of the paper with double spacing and a wide margin. The manuscript should include a title page, abstract, key words, references, tables and legends. The author should retain *a copy for his own use. Manuscripts are not insured against loss or damage.*

The manuscript should be arranged in the following order: 1) title page, 2) abstract, 3) key words, 4) text, 5) acknowledgment, 6) references, 7) author's address, 8) tables, 9) legends for figures.

Manuscripts must be submitted on standard sized manuscript paper. Illustrations and tables should not exceed this size and should be enclosed with the manuscripts.

THE TITLE PAGE should contain, on separate lines, the author(s), institutions and the head(s) of the department, the title of the article, and the name(s) of the author(s). A short title not exceeding 40 letters and spaces will be required for use as a running head and should be written at the bottom of the title page.

THE ABSTRACT should not exceed 150 words and is placed before the text. Reproduction of authors' abstracts is authorized.

KEY WORDS. Four to nine key words for indexing purposes should be given.

TEXT. Papers should be clearly divided into the following sections: Introduction, material, methods, results and findings, discussion. Introduction: the nature of the problem, present knowledge and purpose of the article. Extensive literature reviews are rarely desirable. Primary sources are preferred. Material on which the observations were made. Methods of investigation with sufficient information to permit others to repeat the observations. Results should be supported by statistical analyses when necessary. Discussion should be based directly on the author(s)' contributions within the framework of prior investigations. Unsupported hypotheses should be avoided.

Every page of the manuscript must be marked with the running head including the name of the

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Poul Brændstrup

died January 26 1980 67 years old This is a very great loss for Scandinavian ophthalmology and especially for Acta Ophthalmologica For thirty years Professor Brændstrup was the mainstay of Acta (Managing Editor 1950–1970 Chief Editor 1970–1975 Associate Editor to 1980)

Poul Brændstrup was professor of the University of Copenhagen and head of the Municipal Eye Department of Copenhagen from 1957 He was president of the Danish Ophthalmological Society 1961–1963 and had a great number of honorary jobs because he had the full confidence of all his colleagues

He was Knight of the Dannebrog honoured with the Hjalmar Schiøtz medal and honorary member of the European Ophthalmological Society

His scientific works were profound and original His thesis Congenital Cataract and his works concerning ablatio falciformis vitreous haemorrhage in newborn cystinosis optical aids for partially sighted central retinal vein trombosis and senile cataract are still landmarks in ophthalmological research

Students and ophthalmologists will always remember him as a great and inspiring teacher

Poul Brændstrup died in his home a few hours after having returned from an evening party held with the staff of the hospital in celebration of his retirement

We will miss our dear friend and colleague

Mogens Norn

NEW YEAR - EDITORIAL
K K K Lundsgaard Acta and the Gold Medal

BY

MOGENS NORN

Professor K K K Lundsgaard founded *Acta Ophthalmologica* and in 1931 on his deathbed he established the Acta Prize and Gold Medal The motifs of the medal are described and the first eleven prize winners are mentioned

Key words history K K K Lundsgaard – periodicals Scandinavian Nordic

The cover and title page of *Acta* are decorated with the following words K K K *Lundsgaard edi coepta* This reminds us that Professor Lundsgaard founded *Ac Ophthalmologica*

Who was this Dr Lundsgaard? K K K Lundsgaard (1867 1931) was the four Professor of Ophthalmology of the University of Copenhagen Denmark (19 1931) He had been christened Conrad Christian Carl but preferred K K K C C C to avoid being confounded with a relative (Lottrup-Andersen 1952)

Dr Lundsgaard was a very productive scientist His 180 papers compri practically all subjects of topical interest at that time ranging from surgery ocul lesions and irradiation treatment to historical treatises and papers concerned wi popular science He introduced Credes prophylaxis in Denmark and he particularly remembered for ophthalmo bacteriological publications

Dr Lundsgaard was well known for his organizing ability He was one of th originators – and became President of – the Ophthalmological society of Copen hagen He was elected President of the Danish Medical Society and also of th International Association of Ophthalmologists

Publication of the first Nordic periodical started in 1888 (Nordic Ophthalmological Periodical in Scandinavian Languages) It ceased on economic grounds with the fifth volume in 1892 Scandinavian ophthalmologic papers then had to be publis hed scattered in foreign periodicals or in Scandinavian non-ophthalmological journals

Dr K K K Lundsgaard introduced such a Danish periodical (Dansk Klinik) which however only existed for two years (1909–1911)

In 1911 at the suggestion of Dr Lundsgaard among others a Scandinavian literature ring was established The ring ceased to exist in 1975 after having sent more than 1500 reprints from Scandinavian authors to the members of the ring

This was no satisfactory solution however Dr Lundsgaard therefore at a society meeting in 1919 (Odense) began working for the introduction of a Nordic periodical published in languages of international currency A subscription was started (among 40 Danish ophthalmologists about 50 per cent yielded from 100 00 to 1000 00 Danish crowns each) and he ventilated his idea to the Fifth Scandinavian Congress in 1921 Thanks to the enthusiasm and support with which he met among his Scandinavian colleagues the first issue of *Acta Ophthalmologica* was published in *1923* In this connection there is particular reason to mention Dr Emil Enroth and Dr V Gronholm both Helsinki Finland Dr Sigurd Hagen and Dr Ingolf Schiøtz both Oslo Norway Dr Fritz Ask Lund and J W Nordenson Uppsala Sweden Dr Henning Rønne Copenhagen and as founder and first chief editor Dr K K K Lundsgaard Copenhagen Denmark The latter s private address (Lundsgade 6 København) is seen on the first title page

On August 4 1931 Professor Lundsgaard – just over three weeks before he died – drew up a will in which he donated a fortune intended for a gold medal and a prize to be given at a Scandinavian congress to the author of the best article published in *Acta* The will was addressed to Dr Ejler Holm and Dr H U Møller his two successors The will was rendered translated into German in *Acta* (H U Møller 1936)

We have kept the rough draft with its corrections and the hand written copy Prof Lundsgaard signed the rough draft twice with a shaking hand This was further evidence of Professor Lundsgaard s interest in the continued publication of *Acta* and his desire to encourage future research workers

The *medal* is of gold weighing 59 5 g It is the same size as the Copenhagen University gold medal and carried out by Harald Salomon the Royal Mint According to the testator s wish the observe of the medal is decorated with two owls (Fig 1) a motif from a painting by Adrian Pietersz v de Venne (born in Delft Holland 1589 died in 1662) The small oil painting is still found at *Statens Museum for Kunst* (the State Art Gallery Copenhagen) where Prof Lundsgaard was pleased



Fig 1

Obverse of the Lundsgaard gold medal showing two skating owls wearing spectacles

to see the owls wearing spectacles and enjoyed their remark "How well we are suited to each other" (Hoe dienem wy by een) (catalogue 1922 No 206 from Fredensborg 1905 wood 26 5 × 18 a skating owl couple in peasant dress)

On the reverse of the medal (Fig 2) should be impressed the words *Acta Ophthalmologica Prize* at the testator s wish Dr Ejler Holm (1954) found a spare space for a small relief representing Dr Lundsgaard s profile Note however that it decorates the reverse side of the medal!



Fig 2

Reverse of the Lundsgaard gold medal with relief of Prof Lundsgaard

Table I

Winners of Prof K K K Lundsgaard s gold medal and prize instituted at the Ninth Scandinavian Congress in Stockholm 1935

Gold medalist/subject	Congress	Place	Year	Acta ophthal
Ragnar Granit Helsingfors Finland Electrophysiology retina optic nerve	X	Copenhagen	1938	*16* 658 1938
Thore Lie Thomassen Oslo Norway Glaucoma	XIII	Goteborg	1954	*32* 752 1954
Arne Huggert Umea Sweden Pore size in trabecular meshwork in chamber angle	XV	Oslo	1960	*39* 748 1961
Bengt Rosengren Goteborg Sweden Retinal detachment surgery	XVII	Stockh	1965	*44* 496 1966
Torstein Bertelsen Bergen Norway Fibrillopathia epitheliocapsularis	XVIII	Copenhagen	1967	*46* 612 1968
Arvo Oksala Turku Finland Ultrasonography in Ophthalmology	XIX	Bergen	1969	*48* 832 1970
Torsten Krakau Lund Sweden Regulation of the intraocular pressure	XX	Rekjavik	1971	*Suppl 120* 92 1973
Mogens Norn Copenhagen Denmark Vital staining of cornea conjunctiva	XXI	Helsinki	1973	*Suppl. 123* 945 1974
Niels Ehlers Århus Denmark Graft thickness after penetrating keratoplasty	XXII	Lund	1975	*Suppl. 125* 59 1975
Martin Dalanger Oslo Norway Suspensory apparatus of the lens	XXIII	Copenhagen	1977	*56* 855 1978
Ole I Nissen Copenhagen Denmark Continuous tonometry	XXIV	Oslo	1979	*57* 737 1979

At first the gold medal cost 337 34 Danish crowns and the medal stamps kept at the Royal Mint Copenhagen 1500 crowns The prize amounted to 2000 00 crowns a large sum at that time

The testator decided that the donation may be used to rescue *Acta* itself from possible financial difficulties As soon as the financial circumstances permit the sum is to serve again for the payment of gold medals

Professor Ragnar Granit Finland was the first to be awarded with the gold medal On July 2 1938 Professor M Vannas received the medal in Domus Medica Copenhagen on behalf of the prize winner who was prevented from coming

During the Second World War and the first few years after this Nordic congresses were impossible to carry through The next prize giving did not take place til 1951

The economy of *Acta* the Scandinavian spirit of unity and valuable publications have since permitted Prof Lundsgaard s medal to be given away at nearly all Nordic congresses held so far (Table I)

Recommendations for the reward are to be undertaken by all Scandinavian professors in charge and the President of the Danish Ophthalmological Society There are many publications outstanding enough as to deserve a gold medal The choice may be difficult Further unlike previously many articles and papers are nowadays published by two or more authors But the medal can only be awarded to one author

At the latest editor meeting in 1979 it was decided to raise the Lundsgaard prize appreciably

Professor K K K Lundsgaard was far seeing when he so keenly advocated publication of a Scandinavian ophthalmological periodical At the first turn of the year *Acta* will complete its 57th birthday – a rather considerable age *Acta* thrives well Its economy is in order Nordic ophthalmological science is of an outstanding quality Manuscripts are crowding and the number pages *increases* No less than 14 *supplements have been issued within the last three years*

It will be exciting to study the publications that will appear in *Acta Ophthalmologica* in the course of 1980

Happy New Year!

Acknowledgements

My thanks are due to Mr William Celius Jensen Art Historian and to Professor Poul Brandstrup

References

Acta Ophthalmologica (Kbh) see Table I

Edmund E J (1931) Nekrolog Konrad Kristian Karl Lundsgaard *Hospitalstidende* 74 805

Holm Ejler (1954) Manuskript til prisuddelingen ved nordiske kongres 1951 Goteborg

Lottrup Andersen Chr (1931) K K K Lundsgaard *Ugesk f Læger* 37 933

Lottrup Andersen Chr (1952) Det Oftalmologiske Selskab i Københavns 50 års jubilæum 21 april 1951

Møller H U (1936) Fragen betreffs der Acta Ophthalmologica (Kongresreferat IX Nordisk Kongres 1935 Stockholm) *Acta ophthal (Kbh)* 14 291–297

N O C protocol (Nordisk Oftalmologisk Centralkomite håndskrevet manuskript)

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ELECTRONIC SUBTRACTION METHOD FOR OPHTHALMIC PHOTOGRAPHY

BY

E JAANIO H ALANKO P J AIRAKSINEN H NIEMINEN and S LÄHDE

A commercial electronic subtraction unit orginally intended for the study of roentgenograms was used to produce subtraction pictures of fundus fluorescein angiographies No modifications were needed to make good quality subtraction pictures The method is fast and inexpensive in contrast to previously described photographic methods Certain limitations of the present equipment are discussed as well as some possibilities for further development of the apparatus The method is especially suitable for studies on dynamic processes in the eye and it should prove valuable in the long term follow up of chronic diseases such as glaucoma and diabetic retinopathy

Key words diagnosis – fluorescein angiography – fundus photography – closed – circuit television

Ziedses des Plantes (1935) presented the principles of the subtraction method now in use in roentgenologic angiography The main idea is to subtract the blackness values of one roentgenogram point by point from those of another using the same blackness scale to form a new print in which parts common to both originals are pictured only faintly and differing parts become enhanced It is also possible to compare two frames from an angiography taken at different time lapses and to demonstrate the changes in vascularity that have taken place between the two pictures the so called phase subtraction method (Deininger 1970)

Horiuchi (1971) and Makabe (1972) applied photographic subtraction method for fundus fluorescein angiographies Mikuni & Fujii (1972) used the autosubtraction method to produce a pseudo-relief effect, which helps to interpret the fine

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structure in angiographies The subtraction method was found valuable in the assessment of fundus photocoagulation effects of the retinal edema and retinal vascular fluorescein leakage in central serous retinopathy

The progress in modern videotechnology has made electronic subtraction methods possible Electronic subtraction units based on closed-circuit television (CCTV) are used mainly in roentgenology A common construction principle for electronic subtraction apparatus is the use of two vidicon type television cameras in sync to form video signals from the original pictures The video signals are then amplified by logarithmic amplifiers (Ziedses des Plantes 1968) to preserve the original information of exponential intensity differences Subtraction is achieved electronically by inverting the polarity of one of the video signals and then combining the two signals synchronously The combined video signal now carries information from both original pictures with electronic subtraction and the result can be observed on a television monitor The subtraction picture on the monitor can be changed continuously by the balance and contrast controls which enables quick and smooth study of different grades of subtraction between the original pictures

Photographic subtraction methods are known to be slow complicated and expensive (Deininger 1970 Ziedses des Plantes 1968) which greatly hampers their use in everyday clinical work The subtraction method nevertheless showed great promise in principle and we decided to examine the use of electronic subtraction in ophthalmology since these methods were known to produce good results in roentgenology fast effortlessly and at low costs (Deininger 1970 Ziedses des Plantes 1968)

Material and Methods

The case we chose to present was a 19 year-old female who had had prodromal transient scotomas in the right eye for half a year At the time of the examination she had a permanent field defect of six days duration Ophthalmoscopy revealed an *obstruction in a branch of the superior temporal retinal artery* and a corresponding retinal edema Routine serial fundus fluorescein angiography was immediately performed Later the obstruction disappeared leaving no other traces other than the permanent field defect Figs 2 and 3 were taken at 17 1 second and 30 6 seconds after the injection of fluorescein as seen from the automatic time recorder on the right side in the pictures They were used for subtraction directly in 18×9 4 cm copies which are routinely supplied with the angiography

The copies to be subtracted were placed under each camera of Siemens M 707 A subtraction unit (Fig 1) based on CCTV and necessary adjustments of the camera diaphragms were made The pictures were then moved by hand until they almost

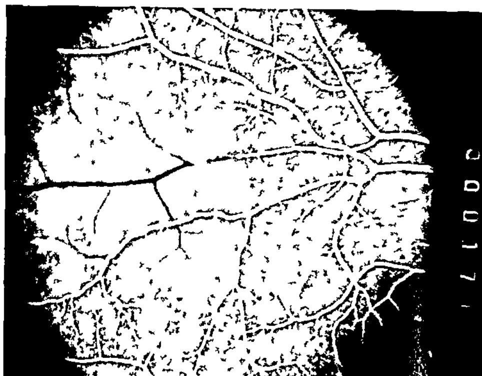


Fig 1
Siemens electronic subtraction unit M 707 A The two video cameras and the television monitor are indicated by arrows The camera at the left produces a normal videosignal The camera at the right produces an inverted negative picture

coincided on the monitor and the fine adjustments of the masking were made by the use of the electronic overlapping controls The correct balance setting was controlled by the use of test charts Subtraction pictures were observed directly on the monitor Pictures to be documented were photographed by a Hasselblad 500 C camera with a Zeiss Planar objective of 100 mm focal length using Kodak Tri X film and 1/5 second exposure time

Results

The subtraction pictures were quite acceptable in sharpness (Fig 4) Phase subtraction made it possible to observe minor changes of fluorescence pattern such



F g ?

Fluoresce n ang ograph of the fundus show ng ret nal artenal branch obs ru t on 17 l seconds after injection Th s p cture s in erted electron cally to ts nega e

as the retrograde filling of the artery (Fig 4) A pseudorel ef effect l ke enhancement of contours was also eas ly obta ned by sl ghtly displac ng the o erlapp ng pictures a phenomenon especially useful in the evaluation of the boundaries of retinal edema (Fig 4) The changes of balance and contrast between the p ctures also add new deta ls of information.

A small part of the ve n below the obstruction at the border of the ret nal edema (Fig 4 sol d arrow) is toned l ghter proving that there has been a local change in the fluorescein concentrat on in this part of the vein starting from a small branch in the edemarons area The change in tone is so small that it is almost mposs ble to observe by comparison of the original angiography frames (F g 2 and 3)

The resolut on in the subtract on picture is naturally inferior to that in the original pictures but it was found quite sufficient for the present purpose The use of higher magnification partly compensates for the lack of h ghest resolut on and enables the study of interesting areas in m nute deta l



Fig 3

A later picture taken at 30 8 seconds A normal television picture was obtained from this photograph

Discussion

The value of subtraction methods in ophthalmology has been evident after the works of Horiuchi (1971) Mikuni & Fujii (1972) and Makabe (1972) but it has gained no wider clinical use Their works were all done by photographic procedures with inherent limitations and it is our belief that this has been the major reason for the poor response that the subtraction method has won in clinical ophthalmology

To our knowledge we are the first to use the electronic subtraction method for the interpretation and analyses of fundus fluorescein angiographies

This method seems to be very suitable for the diagnosis of fundus angiographies Minor changes for this commercial subtraction unit make it still more efficient for ophthalmic use The changes we have introduced now include the use of zoom lenses which will provide variable magnification capability to both cameras to meet the possible discrepancy in the magnification ratio of the copies to be compared With larger magnification it is also possible to compensate for the loss of distinctness in the TV picture



Fig 4

Electronic subtraction picture of Figs 2 and 3 as seen on the television monitor C overlapping of the pictures in the central area The boundaries of the retinal edema clearly shown as well as the retrograde filling of the obstructed arterial tree (open arrow) the filling of a small branch of the vein from edema area (asterisk) Solid arrow points local change in a vein otherwise evenly filled with fluorescein The subtraction picture sh the changes that have taken place in the fluorescein distribution in the fundus during 13 7 seconds between the exposures of the two angiography frames

The principles of subtraction require great uniformity of the pictures to subtracted Changing the photographic angle in fundus photography produ distortions which theoretically should be hard to overcome In practice we fou however that excellent subtraction pictures could be achieved with our method

The electronic subtraction method will help in the diagnosis of routine fluor cein angiographies but we think that the most rewarding use will be found in long term follow up of glaucoma diabetic retinopathy and tumors of the e Comparison of pictures taken on different occasions will be faster and more relia using subtraction Minimal changes of various pathologic conditions in eye can detected earlier a d more easily For recording purposes the subtraction pict can either be phot raphed from the monitor or the information can be stored

videotaping or by the use of special memory units Colorcoding (Fisher 1958) which has been experimentally used in roentgenology may further facilitate perceiving small differences of contrast in the subtraction picture

In a following paper we will report on glaucomatous optic disc changes demonstrated by electronic subtraction

References

Deininger H K (1970) Photograpische und electronische Subtraktionsverfahren in der angiograpischen Diagnostik *Dtch med J 21* 1931–1943

Fisher J F & Gershon Cohen J (1958) Television techniques for contrast enhancement and color translation of roentgenograms *Amer J Roentgenol 79* 342–347

Horiuchi T (1971) Application of Subtraction Method in Fluorescence Fundus Photography *Acta Soc ophthal jap 75* 1019–1026

Makabe R (1972) Anwendung des Subtraktionsverfahrens in der Fluorescenz Fundusangiographie *Ber dtsch ophthal Ges 71* 574–576

Mikuni M & Fujii S (1972) Subtraction Method in Fundus Photography *Acta Soc ophthal jap 76* 1511–1518

Ziedses des Plantes B G (1935) Subtraction Eine rontgenograpische Methode zur separaten Abbildung bestimmter Teile des Objekts *Fortschr Rontgenst 52* 69–79

Ziedses des Plantes B G (1968) Das elektronische Subtraktionsverfahren *Electromedica 1* 23–25

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DEMONSTRATION OF GLAUCOMATOUS OPTIC DISC CHANGES BY ELECTRONIC SUBTRACTION

BY

H ALANKO E JAANIO P J AIRAKSINEN
and H NIEMINEN

We describe a new method the electronic subtraction for objective two-dimensional detection demonstration and recording of glaucomatous optic disc changes Siemens subtraction unit M 707 A based on a double videochain and originally developed for the study of roentgenograms was used The results show that this technique is useful in demonstrating the progressive damage of neural tissue of the disc and associated alterations in the course of the vessels Further development of the electronic subtraction method for glaucomatous optic disc evaluation is discussed

Key words optic disc – glaucoma – electronic subtraction – fundus photographs

Glaucomatous visual field defects are preceded by subtle changes of the optic d and these may constitute the first clinical sign that the intraocular pressure (IO level is not tolerated by the eye (Armaly 1969 Chandler & Grant 1965 Shaff 1969) Therefore a definite need exists for an objective and sensitive method detecting and recording possible glaucomatous changes of the optic discs of patie with ocular hypertension and glaucoma

In this paper we report an electronic subtraction technique for the detection a demonstration of these changes According to the principles of subtraction all pa which are common to original pictures with no difference in size shape or blackn values fade towards the neutral grey but the differing parts become enchanged contrast to photographic methods electronic subtraction is fast and easy perform Details of electronic subtraction in ophthalmic photography have be presented in a previous paper (Jaanio et al 1979)

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Material and Methods

or the present study optic disc stereophotographs of two female patients were elected on the basis of stereoscope findings One patient aged 77 years had been treated for chronic open angle glaucoma for 6 5 years (case 1) The other patient aged 77 years with normal IOP and visual fields but suspect glaucomatous cupping f the left optic disc had been followed for seven years without treatment (case 2) All stereophotographs were taken by the same photographer (H N) with a Zeiss undus camera and Allen stereo separator

In case 1 three pairs of stereophotographs were available with a time nterval of two years between the first and the second photographs and three years between the second and the third photographs In case 2 we had two stereopairs aken 15 months apart For subtraction we used the right hand pictures of each tereopair To avoid unequal magnification and contrast new prints in the same nlargement scale and with equal blackness values were made from the original negatives In case 2 the "earlier picture was inverted electronically to its negative and subtracted from the later" by a Siemens electronic subtraction unit M 707 A imilarly in case 1 the first picture was subtracted from the second and the third picture and the second picture from the third one Resulting subtraction pictures were photographed from the TV monitor of the Siemens M 707 A unit with a Hasselblad 500 C camera

Results

Electronic subtraction shows the differences in two photographs taken of the same object at different times

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Fig 1A to F

Fig 1 A B and C are the right hand pictures of the original stereopairs (case 1) Dates of photography A in March 197? B in May 1974 and C in April 1977 D E and F are subtraction results photographed from the monitor of the Siemens M 707 A electronic subtraction unit D is the resulting subtraction picture between A and B E between B and C and F between A and C

D Disappearance of a small haemorrhage seen in picture A (open arrow) produces a clearly demarcated white area (solid arrow)

E This picture shows the displacement of the small inferotemporal vessel solid arrow points at the original course (white stripe) and open arrow at the new course (black stripe) of the vessel

F The superior arterial branch in the optic disc shows a nasal (solid arrow) and inferior (open arrow) displacement. Pictures D E and F *show clearly the progressive enlargement of the* cupping (i e loss of neural tissue) in the direction of the haemorrhage seen in picture A in contrast to the unchanged superiotemporal neural rim



In case 1 the increasing white infero-temporal area demonstrates the progressive notching of the neural rim (Fig 1D E and F) The gradual displacement of the disc vessels can be seen as deviating black and white stripes (Fig 1E and F) The light streak on the disc border at four o clock position may indicate a change of size or position of the peripapillary pigmentation (Fig 1F asterisk)

In case 2 the lack of contrast indicates that no change had occurred in the contour of the neural rim or location of the vessels during the observation period (Fig 2C)

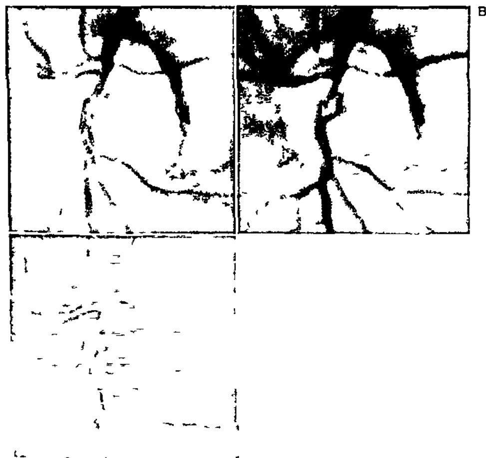


Fig 2A to C

Fig 2 A and B are the right hand pictures of the original stereopairs (case 2) photographed in February 1975 (A) and in May 1976 (B) C is the subtraction result between A and B The unanimous neutral grey and absence of outstanding white areas indicate that no change in the optic disc had taken place during the observation period

Discussion

The methods of detecting changes of the optic disc are inadequate The most common procedure is the comparison of stereophotographs with ophthalmoscopic findings but more accurate objective and faster means for clinical purposes are still lacking

Stereophotogrammetry has been considered a possible solution and adaptations of analogue (Crock 1970 Jonsas 1972 Saheb et al 1972 Portney 1974) analytic (Portney 1975 Kratky 1974) or digital (Kottler et al 1974) techniques for ophthalmology have been reported Crock (1970) supposed that photogrammetry will pass into routine practice but a useful clinical application is yet to come The eye as a part of the imaging system makes stereophotogrammetry of the optic disc complicated (Kratky 1974 Dowman & Elkington 1974) Moreover the atypical imaging geometry of the commercially available fundus cameras does not fulfil the photogrammetric requirements (Kratky 1974)

In contrast to stereophotogrammetric methods electronic subtraction is basically two dimensional and gives no direct information of the cup profile and volume but *selectively produces information of the changes of the neural rim* width which is of major importance in the management of glaucoma

For electronic subtraction no stereophotographs are needed Simple black and white pictures of the disc are adequate and their quality is generally superior as compared with stereoscopic ones In addition photographing through *a smaller pupil is possible If the subtraction unit is not fitted* with zoom-optics the enlargement scales of the original photographs must be equal

The information of the subtraction picture in the monitor is in digitized mode and this enables further handling of the data and the quantitation of the neural rim changes by digital micro computer solutions

The electronic subtraction method is objective and fast and gives a permanent record in the study of photographs of the same optic nerve head taken on different occasions The sensitivity of the method and the quantitation of the results need further studies We think that the electronic subtraction method may prove a valuable contribution to the evaluation of glaucomatous optic disc changes

References

Aramaly M F (1969) The correlation between appearance of the optic cup and visual function *Trans Amer Acad Ophthal Otolaryng* 73 898–913

Chandler P A & Grant W M (1965) *Lectures on Glaucoma* p 13 Lea & Febiger Philadelphia

Crock G (1970) Stereotechnology in medicine *Trans ophthal Soc U K* 90 577–636

Dowman I J & Elkington A R (1974) Photogrammetric measurement of the retina of the eye In Proceedings of the symposium of Commision V International Society for Photogrammetry Biostereometrics 74 pp 972–973 American Society of Photogrammetry Virginia

Jaanio E Alanko H Airaksinen P J Nieminen H & Lahde S (1979) Electronic subtraction method for ophthalmic photography *Acta ophthal (Kbh) 58* 7–13

Jonsas C H (1972) Stereophotogrammetric techniques for measurements of the eye ground *Acta ophthal (Kbh) Suppl 117*

Kottler M S Rosenthal A R & Falconer D G (1974) Digital photogrammetry of the optic nervehead *Invest Ophthal 13* 116–120

Kratky V (1974) Photogrammetric problems in ophthalmologic applications In Proceedings of the symposium of Commision V International Society for Photogrammetry Biostereometrics 74 pp 197–198 American Society of Photogrammetry Virginia

Portney G L (1974) Photogrammetric categorial analysis of the optic nerve head *Trans Amer Acad Ophthal Otolaryng 78* 275–289

Portney G L (1975) Photogrammetric analysis of volume asymmetry of the optic nerve head cup in normal hypertensive and glaucomatous eyes *Amer J Ophthal 80* 51–55

Saheb N E Drance S M & Nelson A (1972) The use of photogrammetry in evaluating the cup of the optic nervehead for a study in chronic simple glaucoma *Canad J Ophthal 7* 466–471

Shaffer R N (1969) The role of astroglial cells in glaucomatous disc cupping *Docum Ophthal (Den Haag) 26* 516–525

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FINDINGS ASSOCIATED WITH GLAUCOMATOUS VISUAL FIELD DEFECTS

BY

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1511 persons *55 to 70 years-old and making up 77% of a population in which* every case of chronic primary glaucoma with visual field defects had remained untreated were comprehensively examined using standardized methods (including *automatic perimetry) and strict diagnostic criteria in order to* assess different methods of identifying the glaucomatous members The prevalence of manifest glaucoma (1%) was unaffected by systemic haemodynamic and vascular disorders In eyes with manifest glaucoma simplex the dispersion of pressures was small and the mean only about 5 mmHg higher than in all eyes Seven out of ten subjects with disc haemorrhages also had glaucomatous visual field defects Other findings causing a suspicion of glaucoma could – as defined here – not have been used to *ascertain* a diagnosis of manifest *glaucoma In 13 out of 15 subjects with glaucomatous visual field defects* an enlarged cup was noted at the initial examination No other method (except automatic perimetry) could – as applied here – have been used to *exclude* the possibility of a manifest glaucoma with an acceptable degree of certainty

Key words glaucomatous visual field defects – disc haemorrhages – *enlarged* optic cup – increased intraocular pressure – anterior segment pathology – family history

On the basis of methods used so far only a small minority of all persons going t develop glaucomatous visual field defects can be identified with a degree precision sufficient to warrant therapeutic intervention prior to *the onset* irreversible function loss (Armaly 1969 1977) For the time being we must dire

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our efforts towards a more effective detection and control of manifest glaucoma (= secondary prevention) For this purpose

"(I) Development of techniques for diagnosing field defects much earlier when randomized controlled (therapeutic) trials might be considered ethical

and

"(II) More detailed study of the factors related to glaucomatous field defects in the general population"

have been proposed as probably the most useful lines of research (Cochrane et al 1968)

The prevalence of manifest glaucoma seems to be much lower than commonly thought (Hollows & Graham 1966) It rises steeply with age but new cases seem to occur at about the same rate from the early fifties on (Bengtsson in press) The incidence is therefore always low – about 0 1% which means that on an average one new case can be expected every year per 1000 persons aged 55 years or more In order to obtain a representative material of manifest glaucoma in early stages a sensitive visual field screening has therefore to be repeated at short intervals in large numbers of subjects comprising all – or a truly representative sample – of the population In order to facilitate an assessment of factors believed to be associated with the occurrence of glaucomatous visual field defects in the general population a more comprehensive examination of each subject should be added to the actual detection of such defects

A study along these lines but on a limited scale was started at the Dalby Community Care Centre (in Southern Sweden) as soon as the most important prerequisite – the automatic perimeter (Heijl & Krakau 1975a b Krakau 1978) – had become available i e a few years ago When it was found that 80% of all cases of glaucoma (simple or not) with visual field defects and in fact every case of manifest glaucoma simplex in the population had remained untreated right op to the initial survey it was realized that an in all essentials representative material of manifest glaucoma in comparatively early stages had been obtained already at the first attempt. The present report of the findings at the initial survey was therefore considered to be justified

Material

All persons born 1907–1921 and resident in the district serviced by the Dalby Community Care Centre were listed in December 1976 The list was arranged according to the residential addresses and kept up to date by means of weekly reports from the authorities on removals and deaths Following this directory the

inhabitants were contacted in rotation during 1977 and 1978 and offered rep ophthalmological examinations Attempts at persuasion were avoided and persons able and willing to attend within a few weeks were included in the surv

One person known to be blind and 24 patients subjected to antiglaucom therapy were not invited There were only five cases with field defects (in congenital and four secondary glaucomas) in this group

Out of 1938 invited persons 1511 (78%) took part in the survey The ra attendance was largely independent of age and sex

Methods

A brief questionnaire concerning medication and general eye symptoms was m together with the appointment notification At the Centre the answers discussed and supplemented with a medical history comprising specific ques concerning diabetes vascular diseases (thromboses haemorrhages and ischaem haemodynamic crisis prodromal symptoms ocular trauma uveitis and fa history

Sphygmomanometric measurements of the systolic blood pressure determ tion of the visual acuity subjective refraction automatic perimetry fundus ph graphy indirect ophthalmoscopy slit lamp examination and Goldman tonom were attempted in every case Apart from the perimeter conventional equip was used in a fairly standardized manner Perimetry and photography conducted by two alternating assistants – ophthalmoscopy slit lamp examina and tonometry by the author Perimetric data handling was entirely automatic other data were immediately recorded on special forms Transfer to magnetic and further processing were performed at the Computer Centre in Lund

The systolic *blood pressure* was measured on the right arm with the subject sitting position

At *ophthalmoscopy* disc haemorrhages large cups notching of the rim (Sp 1978) and vertically oval cups were particularly noted No attempt was mad estimate the size of the disc

The *slit lamp examination* was directed towards the detection of mesench disorders pseudoexfoliations pigment dispersion narrow angles rubeosis ir posttraumatic and (post)uveitic signs

Detailed descriptions of *automatic perimetry* and *optic disc photography* as applie the present study have been given elsewhere (Bengtsson & Krakau 1979)

Criteria

A *glaucomatous visual field defect* (GVFD) was inferred when an "automatic" visual field defect consistent with glaucoma but not explained on other grounds had been reproduced at follow up

A person was considered to suffer from *manifest glaucoma* when a GVFD and a corresponding loss of neural tissue in the optic nerve head co-existed in the same eye This judgement was based on a subsequent comparison of "automatic" field charts and fundus photographs taken at the survey (but not necessarily in agreement with the first impression obtained at the initial examination)

A *family history* of glaucoma was accepted when at least one close relative was reported to have been subjected to antiglaucomatous treatment

A report of *diabetes vascular disease* or a *haemodynamic crisis* was considered notable only if it was based on a clinical judgement prior to the survey

An *enlarged cup* was suspected if a large cup a notching of the rim or a vertically oval cup was observed with the ophthalmoscope at the initial examination

A *disc haemorrhage* on the other hand was not recorded unless its transient nature had been confirmed by repeated photographs

The term *anterior segment pathology* was used to summarize disorders possibly obstructing aqueous outflow detected at the slit lamp examination Gonioscopic findings were not included

Results

The visual field screening resulted in the detection of 20 visual field defects consistent with glaucoma and not explainable on other grounds at the time of the survey One of these defects disappeared within a year and another turned out to be part of a homonymous one The remaining 18 defects fulfilled our criteria for a *glaucomatous field defect* Thus 15 cases (twelve unilateral and three bilateral) with previously unknown glaucomatous visual field defects were identified indepen dently of other factors associated with glaucoma

The glaucomatous visual field defects were found in eyes with notching of the rim (8 cases) a large cup extending to the disc margin (6 cases) or a large cup with a localized undermining of the rim (one case) Thus all eyes with glaucomatous visual field defects also fulfilled our criteria for a *manifest glaucoma*

The numbers of positive answers to our questions concerning *diabetes vascular diseases haemodynamic crisis* and *antihypertensive medication* provided by all subjects and by subjects with glaucomatous visual field defects are listed in Table I A total of 674 such disorders and treatments were reported by 436 out of the 1511 subjects taking

Table I
Number of subjects reporting indicated diseases and medications at survey

	Among all subjects N = 1511	Among subjects with manifest glaucoma N = 15
Diabetes	64	0
Vascular diseases	171	2
Haemodynamic crisis	44	1
At least one of the above diseases	244	3
β-blockers	138	1
Diuretics	213	2
Other antihypertensives	44	0
At least one of the above medications	295	3
At least one of the above diseases and/or medications	436	4

part in the survey Similarly six such diseases and medications were reported four out of the 15 persons in whom glaucoma with field defect was detected at survey Even in the different subgroups the prevalence of manifest glaucoma very much the same as in the whole material (1%)

The distribution of *systolic blood pressures* in subjects with manifest glaucoma closely followed that in all subjects The means were 150 and 153 and the standard deviations 22 and 23 mmHg respectively but the difference was not statistically significant (Student s $t = 0.5$)

Similarly the distribution of *glass refractions* in eyes with glaucomatous visual field defects closely followed that in all eyes The means were +0 7 and +0 9 and the standard deviations 1 3 and 1 9 diopters respectively but the difference was not statistically significant (Student s $t = 0.4$)

The *visual acuity* was reduced (< 0 9) in at least one eye in 120 persons (8%) and about 15% reported *eye trouble* in the questionnaire Among 15 persons with manifest glaucoma two had a reduced visual acuity in one eye caused by nuclear cataract and by a postuveitic membrane on the anterior surface of the lens and reported eye symptoms caused by the cataract mentioned above and by a vertical squint

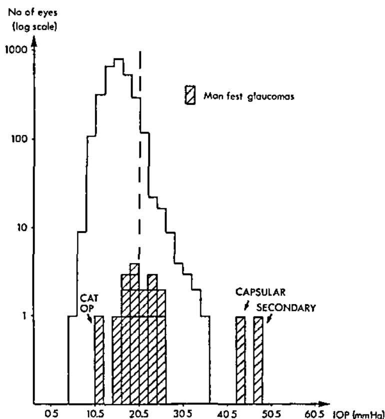


Fig 1

Frequency distribution of intraocular pressures in all eyes and in eyes with glaucomatous visual field defects detected at the survey

The *distributions of intraocular pressures* in all eyes and in eyes with manifest glaucomas detected at the survey are given in Fig 1 If one aphakic eye and two eyes with anterior segment pathology are disregarded the dispersion of pressures of eyes with glaucomatous visual field defects was small and the mean only about 5 mmHg displaced to the right ($\bar{X} \pm$ SD = 20 8 ± 2 9 mmHg)

In ten eyes with disc haemorrhages seven of them with manifest glaucoma the intraocular pressures were similarly assembled but even less displaced to the right ($\bar{X} \pm$ SD = 18 5 ± 2 9 mmHg) The mean pressure was still significantly higher than in eyes of persons without manifest glaucoma ($\bar{X} \pm$ SD = 15 5 ± 3 1 mmHg)

In *normal" persons* (without glaucomatous visual field defects) the *intraocular pressures* were significantly more dispersed and their mean significantly higher in eyes with enlarged cups ($\bar{X} \pm$ SD = 16 8 ± 4 3 mmHg) than in others eyes (F = 2 0 Student s t = 3 0) In eyes with

Table II

Total number of subjects with indicated findings at survey

	Among all subjects N = 1511	Among subjects with GVFD N = 15
Disc haemorrhage	10	7***
Enlarged optic cup	114	13***
IOP > 20 5 mmHg	110	7***
Anterior segment pathology	68	2ns
Family history	73	4 *
At least one of the above findings	313	15 **

ns = not significant
** = significant ($P < 0.01$)
*** = highly significant ($P < 0.001$)

(post)uveitic signs the intraocular pressures were widely dispersed (SD = 8 3 n = 11) an small group contained both the lowest and two out of the six highest pressures obser eyes without glaucomatous visual field defects at the survey Pseudoexfoliations were us unilateral (20 out of 24 cases without glaucomatous visual field defects) and the intrao pressure in the affected eye on an average 2 mmHg higher than in the fellow eye bu significantly higher than in eyes of normal persons without pseudoexfoliations (sinc average of the fellow eye was somewhat lowered) Eyes with other types of anterior seg pathology as well as persons providing a positive family history had intraocular pressures more ordinary distributions

Persons with *disc haemorrhages* (B) *enlarged optic cup* (E) *IOP > 20 5 mmHg* *anterior segment pathology* (G) or a *family history* (H) are considered as glauc suspects The total number of subjects and the number of subjects with GV presenting such findings at survey are given in Table II In all five groups frequency of previously unknown glaucomatous visual field defects was higher t in the whole material The association with manifest glaucoma was statistic significant except in the group with anterior segment pathology but not v strong except in the groups with ophthalmoscopic findings The number of pers with at least one of these five findings i e the total number of suspects remarkably great (313 out of 1511 subjects = 21%) and accordingly the ra e cases with manifest glaucoma among all glaucoma suspects remarkably low (5%)

All types of findings which cause a suspicion of glaucoma were more common women than in men This *sex difference* however was insignificant and restricted subjects with manifest glaucoma in case of ophthalmoscopic findings and larg

dependent on the distribution of pseudoexfoliations (20 women and five men) in case of anterior segment pathology

The relative frequency of enlarged cups and high intraocular pressures increased with age The occurrence of anterior segment pathology was independent of age A family history of antiglaucomatous treatment was furnished comparatively seldom by older persons The *age differences* were statistically significant for enlarged cups as well as for family histories and in accordance with current views on the matter for high pressures

To generalize findings associated with glaucomatous visual field defects were more common in subgroups of the population characterized by a relatively high prevalence of manifest glaucoma For any finding the *variation in degree of association* with glaucoma within the material was therefore less marked – and the statement of a single figure to describe the relation more justified – than if the reverse had been the case

Table III

Number of subjects with indicated combinations of findings (findings not denoted may – but need not – be present) expected (assuming independence) and observed in the present study

	1 Total number of subjects		2 No of subjects without GVFD		3 No of subjects with GVFD	
	Exp §	Obs	Exp §	Obs	Exp §	Obs
BE	0 8	7	0 20	1	6 1	6
BF	0 7	2	0 21	0	3 3	2
BH	0 5	3	0 14	1	1 9	2
EF	8 3	24	6 95	18 *	6 1	6
EH	5 5	9	4 66	5	3 5	4
FH	5 3	6	4 75	4	1 9	2
BEF	0 05	2	0 014	0	2 8	2
BEH	0 04	2	0 009	0	1 6	2
BFH	0 04	1	0 010	0	0 9	1
EFH	0 40	2	0 321	0	1 6	2
BEFH	0 003	1	0 001	0	0 8	1

§ $\text{Exp } XY = n \; \frac{\text{Obs } X}{n} \; \frac{\text{Obs } Y}{n}$ n = 1511 (in col 1) 1496 (in col 2) or 15 (in col 3)

** Highly significant ($P < 0\ 001$)

B = Disc haemorrhage E = Enlarged cup F = IOP > 20.5 mmHg· G = Anterior segment pathology H = Family history GVFD = Glaucomatous visual field defect.

Findings significantly associated with glaucomatous visual field defects i e disc haemorrhages enlarged cups IOP > 20 5 mmHg and positive family histories were markedly associated with each other and the observed frequencies of all possible combinations of them were higher than expected according to the opposite hypothesis (Table III 1) With one exception the association between enlarged cups and IOP > 20 5 mmHg in persons without glaucomatous visual field defects all such *mutual associations* were entirely explained by the associations of the pertinent findings with manifest glaucoma i e the observed frequencies of different combinations in persons with and without manifest glaucoma agreed extremely well the expected ones (Table III 2 3)

Table IV

Number of subjects with indicated combinations of findings (a dash denotes the absence of the finding in question) The number of subjects with glaucomatous visual field defects contained in each group is given within brackets

B	–	–	–	2 (1)
–	E	–	–	79 (2)
–	–	F	–	82 (1)
–	–	–	H	59
Subtotal				222 (4)
B	E	–	–	4 (3)
B	–	F	–	
B	–	–	H	1
–	E	F	–	21 (3)
–	E	–	H	6 (1)
–	–	F	H	4
Subtotal				36 (7)
B	E	F	–	1 (1)
B	E	–	H	1 (1)
B	–	F	H	
–	E	F	H	1 (1)
Subtotal				3 (3)
B	F	F	H	1 (1)
Total				262 (15)

B = Disc haemorrhage E = Enlarged cup
F = IOP > 20 5 mmHg H = Family history

Table V

Conditional probabilities of having a glaucomatous visual field defect if positive – P(GVFD/X) – and of being positive if diseased – P(X/GVFD) – with their 95% confidence intervals

	P(GVDF/X)	P(X/GVFD)
Disc haemorrhage	0.70 (0.35–0.93)	0.47 (0.21–0.73)
Enlarged cup	0.11 (0.06–0.19)	0.87 (0.60–0.98)
IOP > 20.5 mmHg	0.06 (0.03–0.13)	0.47 (0.21–0.73)
Anterior segment pathology	0.03 (0.00–0.10)	0.13 (0.02–0.40)
Family history	0.05 (0.02–0.13)	0.27 (0.08–0.55)

A major part of the glaucomatous visual field defects were accordingly found in subjects with a coincidence of two or more of the four findings significantly associated with a manifest glaucoma in the present population (Table IV). In subjects with only one good reason to suspect glaucoma on the other hand glaucomatous visual field defects were not much more common (1.8%) than in the whole material (1%) (Table IV).

To increase their comparability the frequencies in Table II were transformed into conditional probabilities (Table V)

1) of having the disease if positive P(GVFD/X) = "the diagnostic specificity" and
2) of being positive if diseased P(X/GVFD) = "the nosological sensitivity"

The basic numbers were small and the 95% confidence intervals wide (Table V) but the following observations were considered reliable enough to deserve mentioning.

Seven out of ten subjects with disc haemorrhages also had glaucomatous visual field defects. A disc haemorrhage is therefore a very specific sign of glaucoma. Other findings which cause a suspicion of glaucoma were found to be very unspecific and could as defined here not have been used to ascertain a diagnosis of manifest glaucoma.

In 13 out of 15 subjects with glaucomatous visual field defects an enlarged cup was noted at the initial examination. Simple ophthalmoscopic selection of suspicious cups was thus much and significantly $P \leq 0.025$ (Fisher's exact test) more sensitive than any other method employed here to identify persons with an increased probability of manifest glaucoma. No other method (except automatic perimetry) could *as applied here have been used to exclude the possibility of a manifest* glaucoma with an acceptable degree of certainty.

Discussion

A type of non progressive low tension glaucoma characterized by an acute onset with sudden visual loss and therefore probably greatly overrepresented in self selected materials has been connected with systemic haemodynamic and vascular disorders (Chumbley & Brubaker 1976) In the present more representative material glaucomatous visual field defects were not combined with reduced central visual acuity and not associated with diabetes vascular diseases haemodynamic crises antihypertensive medication or aberrant systolic blood pressures Almost every person deceased after the survey had reported such disorders or medications and it is conceivable – though not likely – that a high mortality could have masked a high *incidence* of glaucoma in persons with a short life-expectancy Anyhow our finding that the *prevalence* of manifest glaucoma was unaffected by systemic haemodynamic and vascular disorders retains its significance in the present conte

Slit lamp examination may be compared with tonometry as a method for t detection of the glaucomas most likely to benefit from current antiglaucomato therapy i e glaucomas with visibly obstructed aqueous outflow and very hi intraocular pressure The present study does not allow of any statements concer ing the relative sensitivities but the rate of persons with anterior segment patholo without visual field defects i e false slit lamp positives" was surprisingly hi (4 5%) Tonometry was in fact the more specific method provided that the upp limit of "normal pressure was raised to 21 5 mmHg

In the present district a majority of patients subjected to antiglaucomato treatment were glaucoma suspects without known glaucomatous visual field defec Congenital acute and secondary glaucomas with glaucomatous visual field defe seldom escaped discovery but persons with similar defects caused by chron primary glaucomas often remained untreated (Bengtsson in press) Many of t "positive *family histories* were therefore accepted on inadequate grounds and the specificity might have been improved e g by an inquiry into the records of t treated relatives if the sensitivity of the family history had not been too low t warrant such an effort Approaching changes in the diagnosis and therapy o glaucoma may call for an early re-evaluation of this point

Any improvement in sensitivity of *tonometry* can be obtained at will simply b lowering the upper limit of normal" pressure but only at the cost of furthe impairments in specificity In the present material for instance tonometry woul have been as sensitive as ophthalmoscopy if persons with intraocular pressur higher than 18 5 mmHg had been considered not "normal" but only at the cost o considering 281 persons i.e 19% of all subjects to be ocular hypertensives

Similarly improvement in the specificity of *cup inspection* is possible by the use o more strict criteria A notching of the rim or a large cup with steep edges extendi

to the outer margin of the disc was noted in ten cases nine with and one without glaucomatous visual field defects The sensitivity could have been restored almost completely by adding persons with disc haemorrhages In fact a notching of the rim a large cup with steep edges extending to the outer margin of the disc and/or a disc haemorrhage were noted at the initial examination in 16 persons, 12 with and four without glaucomatous visual field defects In the three remaining subjects with glaucomatous visual field defects a notching of the rim (two cases) or an extension of a large cup with steep edges to the disc margin (one case) can be observed on the fundus photographs It may therefore become possible to identify persons with manifest glaucoma by *refined disc assessment* with a reliability that approaches that of automatic perimetry (Bengtsson & Krakau 1979)

Disc haemorrhages are fleeting lasting from a few days to several weeks (Begg et al 1971) The observation in a cross sectional survey like the present one of disc haemorrhages in seven out of thirteen cases of simple glaucoma therefore implies not only that disc haemorrhages frequently recur but also that repeated examinations can be expected to reveal disc haemorrhages also in cases of manifest glaucoma simplex which happened to be free from haemorrhage at the initial examination

The present study therefore seems to predicate that disc haemorrhages are not only a very specific sign of manifest glaucoma but also a sign common at one time or another to the vast majority of all persons suffering from simple glaucoma

From a practical point of view this conclusion cannot change the fact that a disc haemorrhage is an elusive sign that often escapes observation

From a theoretical point of view on the other hand the frequent occurrence of recurrent haemorrhages seems to be an important clue to the solution of many problems concerning the pathogenesis of glaucoma The opinion of Drance et al (for references see Drance et al 1977) that the optic neuropathy in this group of patients is probably due to small vessel disease and that an imbalance between intraocular pressure and vascular pressure is not the only cause of visual field defects in glaucoma may be more universally valid than originally understood

References

Armaly M F (1969) Ocular pressure and visual fields *Arch Ophthal (Chicago) 81* 25–40

Armaly M F (1977) *Biostatistical analysis of collaborative glaucoma study* Final report on contract No 1 EY-4 2167

Begg I S Drance S M & Sweenwey V P (1971) Ischaemic optic neuropathy in chronic simple glaucoma *Brit J Ophthal 55* 73–90

Bengtsson B (in press) Prevalence of glaucoma Accepted for publication in *Brit J Ophthal*

Bengtsson B & Krakau C E T (1979) A simple routine for optic disc photography through a natural pupil *Acta ophthal (Kbh) 57* 151–154

Bengtsson B & Krakau C E T (1979) Automatic perimetry in a population survey *Acta ophthal (Kbh)* 57 929–937

Chumbley L C & Brubaker R F (1976) Low tension glaucoma *Amer J Ophthal* 81 761–767

Cochrane A L Graham P A & Wallace J (1968) Glaucoma In Cohen R H L et al (1968) *Screening in medical care* pp 81–88 Oxford University Press London

Drance S M Fairclough M Butler D M & Kottler M S (1977) The importance of disc hemorrhage in the prognosis of chronic open angle glaucoma *Arch Ophthal (Chicago)* 95 226–228

Heijl A & Krakau C E T (1975a) An automatic static perimeter design and pilot study *Acta ophthal (Kbh)* 53 293–310

Heijl A & Krakau C E T (1975b) An automatic perimeter for glaucoma visual field screening and control Construction and clinical cases *Graefes Arch Ophthal* 197 13–23

Hollows F C & Graham P A (1966) Intra-ocular pressure glaucoma and glaucoma suspects in a defined population *Brit J Ophthal* 50 570–586

Krakau C E T (1978) Aspects on the design of an automatic perimeter *Acta ophthal (Kbh)* 56 389–405

Spaeth G L (1978) Morphological damage of the optic nerve In Heilmann K & Richardson K T eds *Glaucoma Conceptions of a Disease* pp 138–156 Georg Thieme Publishers Stuttgart

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COMPUTERIZED MERIDIAN PERIMETRY

A preliminary report

BY

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By a modification of the display of test points it is possible to use the computerized perimeter Competer for meridian testing The test program gives estimates of the thresholds in two separate rounds the second starting when the first is completed Accordingly two profiles are plotted in the meridians tested Furthermore a smoothed profile is drawn from the mean values of the two rounds The outcome when testing normal subjects and cases with glaucomatous defects was studied and the stability of thresholds in normals and the decay in scotomatous areas with time is demonstrated

Key words computerized perimetry – static profiles – time dependence

Manual static perimetry is generally practiced by plotting the thresholds at points along a meridian passing through a scotomatous area In its first version our automatic perimeter was provided with the lights placed along a meridian but the number of test points were few and this apparatus merely served the purpose of studying the conditions precedent for computerized perimetry In the present note we want to describe a version of the automatic perimeter "Competer" intended for plotting meridians in clinical cases

The results of testing normal and pathological cases will also be touched upon

Apparatus

The design and general appearance of the apparatus as well as its electronic parts are the same as previously described (Heijl & Krakau 1976) except that a number of

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It is possible by a simple change of the orders to the computer to determine the extension of the meridians tested and even to exclude one of the meridians from testing. In the present study the limit was put at ± 15 degree in both meridians. The time required for one session was 13–17 min, the mean of the normal group being 13 30 and that of the pathological group 14 45.

Both the normal group and in all glaucoma cases the meridians 45–225 degrees and 135–315 degrees were tested.

The background illumination was 0 1 cd/m² for five patients treated with miotics and 1 0 cd/m² in all other cases.

Fig. 2 shows the outcome of two test sessions in a normal subject. The threshold values of the rounds after one and three changes of sign follow each other closely. At most points the difference is ≤ 1 step, exceptionally it amounts to two steps.

For comparisons between the outcome of different test sessions in the same subject a simple measure of performance (P) has proved valuable. It is the sum of

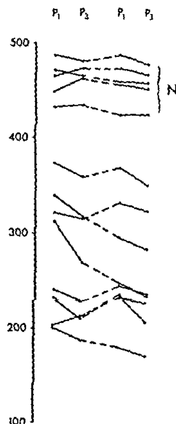


Fig. 3

P values from the first (P'1 and P'3) and second session (P''1 and P''3). N normal group

the estimated threshold values of all points tested ($P = \sum_{1}^{N} x$). P is automatically calculated at the end of a session.

The programme described produces two P values in each session, one from the first change of sign (P_1) and one from the 3rd (P_3).

As seen in Fig. 3 the P values show a small variation in the normal subjects. There is no significant trend towards lower values in P_3 than in P_1 as was shown by means of a simple sign test.

In order to test the significance of the differences in performance between the various rounds we presume that the random variation of the threshold estimates is similar at all tested points. The series of differences between the thresholds of each point of two rounds to be compared is formed. The hypothesis that the differences of these paired observations do not on the average differ from zero was tested by means of the sign test. There was no significant difference (on the 5 per cent level) in any of the normal cases between the two rounds in the same session or between the same rounds in different sessions. The mean differences ($P_1 - P_3/60$ etc.) which are $\leqq 0.22$ thus fall inside the random variation of the measurements.

As must be expected the differences of the dispersions in the mean value series are considerably smaller than in the primary series. In agreement with previous results (Holmin & Krakau 1979) it is concluded that the results are fairly stable at repeated testing of normal subjects.

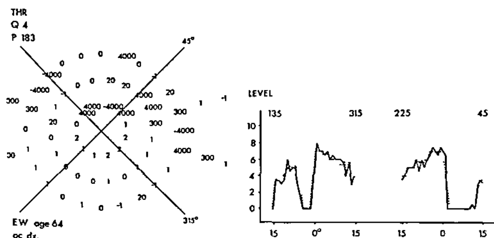


Fig. 4

A. Visual field obtained with circular pattern system and threshold programme showing defects in the upper part (glaucoma spl.)

B. Meridians (mean profiles) through the defects. First session fulldrawn, second session dotted lines.

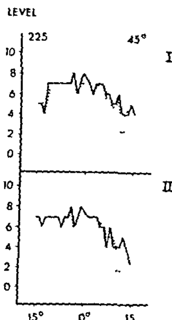


Fig 5

Deepening of relative scotoma in a case of glaucoma spl from first (fulldrawn) to t (dotted) change of sign rounds Note that the normal parts of the profiles remain practi unchanged Similar pattern in both sessions (I and II)

In *pathological* cases meridians are chosen so as to cut through scotomata (Fig 4) the present group it occurred that the same meridians as those tested in the nor group were most appropriate) Accordingly the P values are lower in the pathol cal group than in the normal one The values are also often less stable and show all sessions but one a tendency to decay with time (i e $P_3 < P_1$) This is in fac accordance with previous findings among glaucoma cases using long session tes (Holmin & Krakau 1979) The dispersion of the point to point differences betw the first and second sessions or between the two rounds in a session are as a r higher than among the normal which indicates that the change in performanc not merely a general change of level This is also very clear at inspection of meridian plottings the parts falling in scotomata are as a rule less stable than normal parts of the meridians (Fig 5 and 6) The hypothesis of homoscedasticn the tested points is therefore not tenable in scotomatous fields

When the whole set of test lights has to be used it is likely that the program described may be found too time-consuming and a simpler version may preferred By a few order in the language "Basic" is easily achieved that the t process ends after the first change of sign One may also ask if there are any reas at all to go on testing until the third change of sign The gain might be that a m

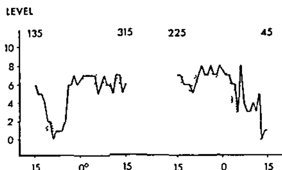


Fig 6

Scotoma increase in a case of glaucoma spl from first (fulldrawn) to second (dotted) session Normal parts remain practically unchanged

curve from the first and the 3rd round can be formed and this smoothes random irregularities Furthermore when it comes to pathological cases it may be a piece of valuable information that a defect is provoked or increased when the testing is extended in time

We conclude that the system for automatic meridian perimetry described has a density of test points along the meridians which makes it well suited for the tracking of defects For the follow up of defects good help is rendered by the performance measure P which compresses information of a profile into a single number Ordinary statistical tests are applicable to a series of such performance values and the degree of significance in a suspected progress can be assessed

Acknowledgement

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References

Heijl A & Krakau C E T (1975) An automatic static perimeter design and pilot study *Acta Ophthal (Kbh)* 53 293–310

Holmin C & Krakau C E T (1979) Variability of glaucomatous visual field defects in computerized perimetry *Albrecht Graefes Arch. klin exp Ophthal 210* 235–250

Krakau C E T (1978) Aspects on the design of an automatic perimeter *Acta Ophthal (Kbh) 56* 389–405

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ULTRASONIC INVESTIGATION OF THE EYE WITH A NEW CONTACT METHOD AND WITH THREE DIFFERENT REAL TIME PRESENTATIONS

BY

ARVO OKSALA, MAURI LUUKKALA and PEKKA MERILÄINEN

The ultrasound examination was carried out by means of a crystal with a 40° sector scan which was pressed either against the eyelid or directly against the sclera The real time display was obtained by either A mode B mode or combined A/B mode scanning In clinical applications both the resolution capacity and the sensitivity of the device were good A mode scanning gave the greatest accuracy in amplitude measurement while the A/B mode yielded the most concrete topographic picture of the target

Key words ultrasonography – contact method – real time presentation

The use of ultrasound in ophthalmic diagnostics began during the 1950s (Mundt & Hughes 1956 Oksala & Lehtinen 1957 Baum & Greenwood 1958) The two first mentioned investigators who used A mode ultrasound published only one paper on the diagnostics of intraocular tumors In the late 1950s and early 1960s Oksala & Lehtinen concentrated on the development of the A mode Baum & Greenwood on that of the B mode In the late 1960s and particularly during the 1970s the advantages and disadvantages of the two methods were studied in many research centers and their clinical usefulness was found to be greatest when they were used to complement one another

One major practical problem in B mode examination has been the necessity of the water bath between the transducer and the eye To eliminate this necessity Bronson developed (in 1967) the first hand held scanner for the B mode examina-

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of the eye and orbit In this procedure a case within which the transducer is ing is usually pressed against the eyelid During the 1970s this procedure has ed increasing application because of its simplicity

the following paper we present a new examination device using a hand held ner which is pressed either against the eye lid or directly against the surface of eye and which permits A B and A/B mode examinations

Methods

1 shows the device on the left at the top of the cable lies the transducer h during the examination either stands still (A mode) or performs a sector of 40° (B or A/B mode)

hand held scanner head of this device consists of the transducer a DC motor and a hanism to transform the rotational motion of the motor into a sector-scanning motion of transducer In addition a simple optical sensor is coupled to the motor axis to generate a al to produce a synchronous sweep on the display tube The scanning mechanism results in usoidal movement of the transducer as a function of time The scanning rate is variable a rate of about 20 frames seems to be optimum when a pulse repetition rate of 3 kHz has used

he active element of the standard transducer is a focused 6 MHz piezoelectric PZT 5A tal with focal length of 24 mm and diameter of 6 mm The crystal is backed and covered impedance matching layers in the conventional manner A typical bandwidth of 40% been measured for the transducers This means an axial resolution of about 0.5 mm h is in agreement with the experimental results The maximum lateral resolution is ined at the focal distance i e in this case at the front of the retina and it has been found e likewise 0 5 mm

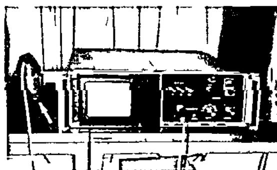


Fig 1

The new ultrasound equipment On the left an arrow indicates the transducer

This ultrasonic ophthalmic scanner has three real time display modes In addition to the conventional A and B mode there is a third one which we call the A/B mode This mode displays a quasi three dimensional synthetic perspective image of the tissue under examination containing simultaneous information about the anatomical features of the cross section and echo amplitudes with all the dynamic capacibility of the A mode However part of the information is lost by the partial overlapping of the echo signals A HP 1333 display tube with 80 × 100 mm² frame size has been used as a display element so far but will be replaced by a HP 1337A memory tube with variable persistence The pulser amplifier electronics of the device follow standard solutions An internal electronic caliper for the measurement of various distances in all three modes is included The number of panel controls has been kept to a minimum A more detailed description of the mechanical structure and electronics of this ultrasonic ophthalmic device has been published (Merilainen & Luukkala 1979) The industrial production of the device will be started Lasertek Oy Helsinki Finland

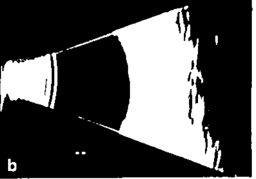
The eye and orbit of a patient is examined after anesthetization with a drop pressing the transducer either against the eyelid or the sclera In an axial A scan the immovable transducer is pressed against the centre of the cornea while an axial B mode or A/B mode scan the moving transducer is pressed against eyelid and the sector scanning occurs through the lens In the diagnosis of d of the eye and orbit past the lens A mode B mode and A/B mode examina are carried out chiefly by lightly pressing the transducer directly against the sc or by pressing it against the eyelid and aiming the beam at the desired point in eye or orbit

Results

Echograms of a healthy eye

Fig 2 shows echograms of a healthy eye resulting from A mode (Fig 2a) B-mode (Fig 2b) and A/B mode scanning (Fig 2c) On the left is the transmitter impulse followed by an acoustically homogeneous space representing the vitreous body on the right we see the echoes from the fundus of the eye and from the retrobulbar tissues The vitreous body of the healthy eye of a young or middle aged subject is shown by modern techniques to be acoustically homogeneous Fig 3 shows the echograms of the degenerated vitreous body of an old person In the A mode one or more echoes are reflected from the vitreous body and their location and amplitude vary rather quickly (Fig 3a) In the B mode these echoes take the form of spots varying in number and location as well as a slight variation in luminance (Fig 3b) In the A/B mode the degeneration of the vitreous body appears as a series of peaks of varying amplitude location and number whose amplitude can be measured with an amplification control device equipped with a decibel scale (Fig 3c)





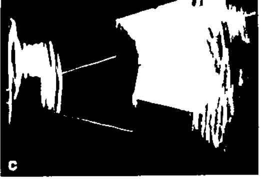
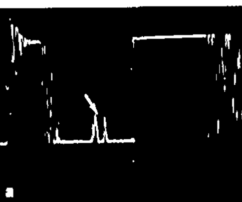


Fig. 2

A n le B n le an I A B n ode p t res f a yo ng I eal ly eye The v re s bo ly s a lly homogenec s



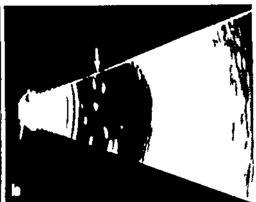




Fig 4

Echograms of retinal detachment by means of A mode (a) B mode (b) and A/B mode (c) An R indicates echoes from the retina and arrows echoes the vitreous degeneration N shows the optic nerve

Fig 5

Echograms occuring in some eye diseases

The echograms of an idiopathic detachment of the retina are shown in Fig 4 An A mode scan (Fig 4a) shows that the echo from a detached retina is considerably higher than those reflected from the degeneration of the vitreous body In B mode scanning (Fig 4b) the detached retina appears as a nearly continuous series of light points which in case of a central detachment is attached to the papilla In A/B mode scanning (Fig 4c) the detached retina appears as a steep chain of peaks the vitreous degeneration as a series of separate echo peaks (indicated by an arrow) and in this figure the relatively homogeneous subretinal fluid as an acoustically empty space

The echograms of a choroidal melanoma are also highly characteristic In A mode scanning (Fig 5a) relatively high and static echoes which reach the fundus are reflected from the area of the tumor In B mode scanning (Fig 5b) the echoes from the tumor area are not as close together as in the A mode but a simultaneous detachment of the retina is clearly observable In A/B mode scanning (Fig 5c) the echoes reflected from the tumor are more frequent than in the B mode and their amplitude is measurable in decibels A possible simultaneous detachment of the retina if the beam hits it is observable as a series of echoes as seen in Fig 4c

If much blood has penetrated into the jelly like vitreous A mode scanning (Fig 6a) shows numerous high echoes reflected from the vitreous space Using the A/B mode (Fig 6b) the localization of the haemorrhage is shown in the sector examined and also the great variation in echo amplitude In Figs 6a and b the echoes reflected from the haemorrhage are lower in the anterior part of the vitreous body than in the middle and posterior part

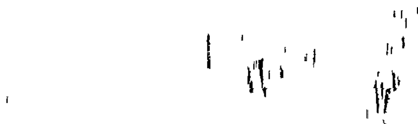


Fig 6

Vitreous haemorrhage can reflect different kind of echoes often with high amplitudes as seen by A mode (a) and also over large area as seen by A/B mode (b) H shows the haemorrhage

Discussion

Compared with many earlier ultrasound devices used in ophthalmological examination the device presented offers certain clear advantages the frequency of 6 MHz and the focusing give the device both good resolution capability and sufficient sensitivity The latter means among its other consequences that the vitreous degeneration caused by aging and the acoustic heterogeneity of the subretinal space in cases of detachment of the retina are usually observable The device also makes possible to diagnose diseases of the orbit up to about 2 5 cm from the rear eye wall Various measurements of the eye and orbit can also be performed with a accuracy of ± 0 5 mm

The possibility of performing an examination in A mode B mode and A/B mode makes the quantitative and topographic analysis of the echograms relatively exact The amplitudes of the echoes can be measured with a decibel scale most precisely with the A mode but the same measurement is also possible with the A/B mode which indicates topographic conditions more accurately This kind of measurement is clearly more exact than when the grey scale alone is used In our experience the A/B mode gives a more concrete picture of both the healthy and pathological eye than the B mode alone

The examination is easy to carry out by pressing the transducer lightly either directly against the eye or against the lid When the eye is examined through the sclera the sector scanning causes a slight movement of the conjunctiva which however has not been found to cause any harm to the eye After routine clinical use of the procedure for almost two years not even conjunctival sugillation has been observed

The localization is more accurate if the transducer is pressed against the surface of the eye rather than against the lid because the position of the beam inside the eye can then be better estimated When the transducer moves across the surface of the eye the topography can be described more precisely than with the immersion method where a water column lies between the transducer and the eye If the eye is in a water bath during the examination we can also see the echograms from the anterior parts of the eye such as the cornea and iris but cases where such an ultrasound examination is really needed are very few

The small size of the examination device and its easy handling make it suitable for use wherever eye diseases are diagnosed and treated In the examination of the vitreous space even when optical examination is possible we often get information by means of ultrasound from a considerably larger area than would be possible optically In vitrectomy where the immersion method can not be used this kind of ultrasound examination is easy and aseptic

References

Baum G & Greenwood I (1958) The application of ultrasonic locating devices to ophthalmology theoretical considerations and acoustic properties of ocular media. (I) Reflective properties *Amer J Ophthal 46* 319–329

Baum G & Greenwood I (1958) The application of ultrasonic locating techniques to ophthalmology *Arch Ophthal (Chicago) 60* 263–279

Johnson N R Fisher Y L Pickering N C & Travner E M (1976) *Ophthalmic Contact B Scan Ultrasonography for the Clinician* p 4 Intercontinental Publications Inc Westport.

Kilamen P & Luukkala M (1979) Ultrasonic Ophthalmoscope *Acta Polyt Scand* Applied Physics Series Ph 124

Mundt H & Hughes W F (1956) Ultrasonics in ocular diagnosis *Amer J Ophthal. 41* 488–498

Oksala A & Lehtinen A (1957) Diagnostics of detachment of the retina by means of ultrasound *Acta ophthal (Kbh) 35* 461–467

Oksala A & Lehtinen A (1957) Über die diagnostische Verwendung von Ultraschall in der Augenheilkunde *Ophthalmologica 134* 387–395

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ABSORBABLE SUTURES (DEXON AND VICRYL) IN THE CORNEOLIMBAL INCISION

Used in lens implantation surgery

BY

NIELS VESTI NIELSEN JENS CARL HØJBJERG and ERIK WESTERLUND

In 115 consecutive cataract extractions with implantation of arteficial lens a clinical evaluation of absorbable sutures polyglactin (910) (Vicryl® 7-0) and polyglycolic acid (Dexon® 8 0) – in corneolimbal incision has been performed The corneolimbal wounds were closed by continuous suture technique with one double loop knot at the 12 o clock and 5-6 loops on each side of the 12 o clock knot The suture had disappeared after 8 weeks in 95% of the eyes
Two months after operation the visual acuity the power of corneal astigmatism and astigmatic orientation remained unchanged in both the Vicryl® and the Dexon® sutured group This provided effectuation of early full prescription of glasses
Most complications in this material were suture independent and appeared during the early postoperative period In only one eye indequate wound closure was noticed Shallow anterior chamber and hypotonia of short duration occured in 5 eyes Four of these patients developed corneal dystrophy
In the Vicryl® sutured group suture reactions took place in 87% of the eyes With dexon® suture no such reaction appeared
The use of absorbable sutures in corneolimbal incision technique implies several surgical advantages and is seemingly safe

Key words lens implantation surgery – absorbable sutures (Dexon® 8 0 Vicryl® 7 0) – corneolimbal incision – corneal astigmation – complications

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n recent years the advantages of the synthetic absorbable sutures polyglactin 910 Vicryl®) and polyglycolic acid (Dexon®) in ophthalmic surgery have been emonstrated in several studies (Bartholomew et al 1976 Blaydes 1979 Dunlap et l 1976 Furgiuele 1974 Sherman 1979 White & Parks 1974 Williamson 1974) However Klemetti (1979) recently has reported frequent complications using Dexon® 7 0 in corneoscleral incision of cataract operations

At the present the properties of these sutures in corneal or corneolimbal surgery have not been reported

The aim of this study has been to estimate the efficacy and safety of resorbable utures in corneolimbal incisions performed in lens implantation surgery

The reasons for the application of this surgical technique in our department have been the requirements of obtaining an improved operating field during mplantation of clip lenses by avoiding a conjunctival flap reducing the frequency of haemorrhages during surgery rendering the late removal of permanent sutures superfluous and providing an early prescription of definitive glasses post operatively

Material and Methods

The material comprised 115 consecutive intracapsular cataract cryoextractions with implan ation of an iris clip lens (Federow modification of iris clip lens) in 100 patients

Vicryl® sutures were used in 60 eyes of 50 patients (22 women and 28 men) with a mean age of 76 years (range 61–91 years) from June 1977 to April 1978 Thereafter Dexon® sutures were applied in the following 55 eyes of 50 patients (19 women and 31 men) with a mean age of 74 years (range 64–89 years) until December 1978 All patients had a senile cataract Patients with corneal dystrophy shallow chamber significant iris atrophy uveitis glaucoma diabetes mellitus and retinal vascular occlusive disorders were excluded from lens implant surgery

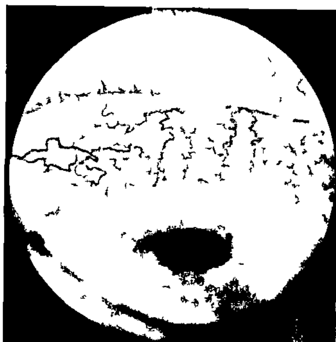
In 80 cases the operation was performed by the chief surgeon and in the remaining 35 cases by the second surgeon

Preoperatively 500 mg acetazolamide was administered intravenous in order to lower the intraocular pressure All operations were performed in local anaesthesia Both surgeons used operating spectacles with a 2 × magnification

The surgical technique was unchanged in this material A corneolimbal incision in front of the limbal blood vessels with an extent of 180 was made with a preplaced suture localized at 12 o clock A perforating incision about 5 mm in extent to the anterior chamber firstly was performed with a knife (razor blade) Thereafter the incision was widened with a corneal scissor perpendicular to the corneal surface Two iridectomies at the 10 and 14 o clock position were made

The wound was closed by continous sutures (Vicryl® 7 0 or Dexon® 8-0) with 5-6 loops on both sides of the 12 o clock position where a double knot was primarily tied (Fig 1) Finally the continuos sutures were tied with an unburried knot at the 9 and 3 o clock positions

Postoperatively the patient were treated with prednisolon eye drops 3 times daily for 2 months and pilocarpine 2% eye drops for half an year 2 times daily



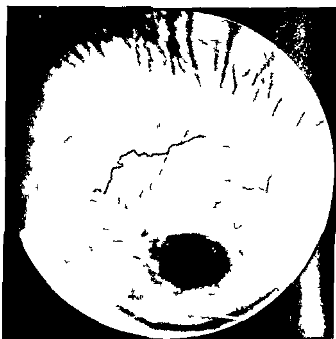


Figure 1a and b

A corneolimbal wound continuosly sutured with Dexon® 8-0 In 10 d vs a vascula pannus has developed from the limbal region (Fig 1a) The sutures have d sappeared af weeks (Fig 1b)

Before cataract operation corrected visual acuity slitlamp examination intraocular pres-e by Goldmann s applanation tonometry and ophthalmoscopy were registered Postope ively the patients were controlled daily in the first 10 days and regularly 1 month and 2 nths after operation A final reexamination took place after 6 months in the Dexon® ured group and 15 months in the Vicryl® sutured group On these controls corrected ual acuity corneal astigmatism and axis by Javal Schiotz keratometry and intraocular ssure were recorded Rupture and disappearance of sutures and any complications after eration were evaluated by slitlamp examination and ophthalmoscopy

atistical Methods

e results were evaluated by using chi-square test and Mann Whitney rank sum test.

Results

sual acuity corneal astigmatism and intraocular pressure

appears from Table I that a definite improvement of corrected visual acuity cured already after 2 months ($P < 0.001$) At follow up examination no gnificant change in final corrected visual acuity was observed compared to the sults obtained at 2 months of observation ($P < 0.10$) A final visual acuity ≤ 6 9 67) was obtained in 70% of the patients (72% in the Vicryl operated and 68% in e Dexon operated group)

Concerning postoperative examinations of corneal astigmatism and the axial ientation (Tables II and III) it is noted that no significant changes of these values e appearing at the 2 months control ($P < 0.10$) In both groups the final ientation of the axial orientation of corneal astigmatism was against the rule icryl® 87 6 g and Dexon® 82 1 g)

Table I

isual acuity pre and postoperative in 60 Vicryl® and 55 Dexon® sutured eyes No further improvement of visual acuity is occurring on follow up examinations (P < 0 01)

		Pre-op	10 days	1 month	2 months	follow up
Visual acuity mean (± SD)	Vicryl	0 15 (0 17)	0 29 (0 18)	0 46 (0 27)	0 67 (0 29)	0 70 (0 30)
	Dexon	0 23 (0.22	0 37 (0 29)	0 53 (0 28)	0 69 (0.30)	0 73 (0.31)

Table II

Postoperative power of corneal astigmatism in 60 Vicryl® and 55 Dexon® sutured eyes astigmatism is insignificantly changed after 2 months ($P < 0.01$)

		10 days	1 month	2 months	Follow-[illegible]
Corneal astigmatism	Vicryl	4.12 (1.60)	3.80 (1.48)	3.52 (1.41)	3.1 (1.31)
mean (± SD) Δ K (diopt)	Dexon	5.80 (2.54)	3.60 (1.60)	2.91 (1.40)	[illegible] (1.5[illegible])

Cicatrice and disappearance of sutures

Repeated inspections of the cicatrices disclosed no inadequate wound heal[illegible] except in one case (Table IV) In Fig 1 the wound and continuous suture in [illegible] corneolimbal incision is illustrated 10 days and 8 weeks after operation. Afte[illegible] weeks the sutures (both Vicryl® and Dexon®) had ruptured and were disappear[illegible] in 95% of the patients. In none this occured before 4 weeks In all eyes we no[illegible] various ingrowth of a small vascularized pannus from the limbal region to [illegible] cicatrice This zone of fibrovascular tissue persisted until the sutures disappear[illegible] In 40 patients (46 eyes) sutured with Vicryl® an annoying foreign body sensa[illegible] with various hyperaemia and mucus secretion occurred Dexon® sutures did [illegible] cause such a reaction

In no patient was the development of pathological corneal excavations at [illegible] corneolimbal cicatrice observed.

Table III

Postoperative axial orientation of corneal astigmatism in 60 Vicryl® and 55 Dexon® sut[illegible] eyes. Already after 10 days the astigmatism in the Dexon® group is orientated against [illegible] rule. One to two months after operation no further significant shift of the axial orientation [illegible] noted ($P < 0.10$)

		10 days	1 month	2 months	Follow-[illegible]
Axial orientation of corneal astigmatism	Vicryl	62.9° (44.8)	81.4 (32.5)	84.0° (21.[illegible])	[illegible] (1[illegible])
mean (± SD)	Dexon	78.6° (45.2)	79.5 (33.9)	80.5 (18.[illegible])	[illegible]1 (1[illegible])

Table IV

Postoperative complications in 60 Vicryl® and 55 Dexon® operated eyes. The number of eyes with late presence of shallow anterior chamber, hypotonia and corneal dystrophy (right column) have continued complicated from the early postoperative period. No significant difference of complications between the Vicryl® and Dexon® group was disclosed ($P < 0.10$)

Complications (number of eyes)	Suture					
	Vicryl			Dexon		
	During surgery	Early ≤ 10 days	Late > 10 days	During surgery	Early ≤ 10 days	Late > 10 days
Hyphaema	2	4		1	2	
Vitreous loss				2		
Dislocation of lens implant		1		1	2	
Inadequate wound closure					1	
Shallow anterior chamber		2			3	1
Hypotonia (< 9 mmHg)		8			11	1
Hypertension (> 22 mmHg)			4			3
Uveitis		1			3	
Pupillary exudate membrane						1
Corneal dystrophy		2	2		2	2
Macular oedema			1			2

Complications

Early and late complications are listed in Table IV. It is noted that both shallow chamber and ocular hypotonia with cornea lens implant contact appeared in 5 patients with a duration of 1 to 2 days. In these cases no obvious leakage of aquous humor from the cicatrice was disclosed by Seidel's test. Inadequate wound closure appeared in one eye because of sutures placed too superficially, which in few days cut through the corneolimbal tissue. A sufficient closure was obtained by resuturing the eye.

Discussion

The results of this study indicate that the resorbable sutures polyglycolic (Dexon® 8 0) and polyglactin 910 (Vicryl® 7 0) are useful for suturing corneal incision in lens implant surgery

The main difference between the applied sutures was the appearance of s complaints in the Vicryl® sutured group

Considering the healing of the corneolimbal wound we noted an early form of a superficial vascularized granulation tissue from the vessel arcades of lir Presumably this accelerates the corneal healing and provides the efficacious u absorbable sutures in the corneolimbal region

In experiment on the rabbit cornea it has been demonstrated that co wounds at limbus heal faster than more central placed corneal wounds (Gas Dohlman 1968) Thus a significant higher tensile strength of the perip corneal wounds in rabbits was obtained already after 12 days It is possible tha absorbable sutures used in our series further stimulate the formation of fibrovascular tissue in the corneolimbal wound Flaxel & Swan (1969) have stu the limbal wound healing histologically in human aphacic eyes They observed a remodelling of the corneal wound first took place after 46 days According time of resorption of the sutures in the present series as in other studies (Dunl al 1976 Bartholomew et al 1976 Furgiule 1974) coincides with both the time high corneal tensile strength and the remodelling of the wound (Gasset & Doh 1969 Flaxel & Swan 1969) However Condon & Hill (1973) have in experim animal studies shown that a critical and direct suture dependent phase of co wound healing is present during the first 6 days after incision Vicryl® 11 0 su used in central corneal wounds in rabbit obvioulsy remain intact for only 1S (Faulborn & Theopold 1977) It must however be assumed that only mi absorption and decrease in tensile strength of Dexon® 8 0 and Vicryl® 7-0 co sutures are appearing in this early phase (Craig et al 1975) However fu studies of the tensile strength of Dexon® and Vicryl® in corneal wounds are nee It is remarkable that no rupture of Dexon® 8 0 or Vicryl® 7 0 used in our ma occurred within the first month after operation

Concerning the power of corneal astigmatism and the axial orientation noteworthy that no significant changes occurred 2 months after operation Dexon® and Vicryl® This practically implies that early full prescription of g can be performed contrary to suture techniques with a non resorbable s nylon 10 0 (Thygesen et al 1979) However the power of the final astigmati our material appeared to be about 1 Diopter higher (Thygesen et al (1979)

In Klemetti s series (1979) a notable high frequency of suture depe complications appeared after suturing corneoscleral wounds with Dexon®

hese frequent complications however have not been demonstrated by others Bartholomew et al 1976 Blaydes 1979 Furgiule 1974 Sherman 1979 White & arks 1974 Williamson 1974) Moreover the majority of the complications in lemetti s material (1979) occured 22-42 days after operation In our material most omplications probably were suture independent and appeared during the early ostoperative course (≤ 10 days)

References

aggesen L H Land A M & Nielsen N V (19 7) Results from lens implantation A material from four danish hospitals *Acta ophthal (Kbh) 55* 414–421

artholomew R. S Phillips C I & Munton C C F (1976) Vicryl (polyglactin 910) in cataract surgery *Brit J Ophthal 60* 536–538

lavdes J E (1979) An evaluation of 8-0 polyglycolic acid braided synthetic absorbable suture in cataract surgery *Ann. Ophthal 11* 963–965

ondon P I & Hill D W (1973) The testing of corneal wounds stitched with modern corneo-scleral sutures experimental corneal wound healing *Ophthal Res 5* 137–150

raig P H Williams J A Davis K W Magoun A D Levy A J Bogdonosky S & Jones J I (1975) A biologic comparison of polyglactin 910 and polyglycolic acid synthetic absorbable sutures *Su g Cynec Obstet 141* 1–10

Dunlap W A Purnell W D & Mc Pherson S D (1976) New synthetic absorbable suture for ophthalmic surgery laboraty and clinical evaluation *South Med J 69* 588 59?

Faulborn J & Theopold H (1977) Experimentelle Studien uber Prolene 10-0- und Vicryl 11 0-Nahtmaterial im Vergleich zu Nylon 10-0 an der Kaninchenhornhaut *Kl n Mbl Augenheilk 170* 605 613

Flaxel J T & Swan K C (1969) Limbal wound healing after cataract extraction *Arch Ophthal (Chicago) 81* 653–659

Furgiuele F P (1974) Ophthalmic use of a new synthetic suture (Dexon) *Ann. Ophthal 6* 1219–1225

Gasset A R & Dohlman C H (1968) The tensile strength of corneal wounds. *Arch Ophthal (Ch cago) 79* 595–60?

Klemetti A (1979) Late complications of 7-0 polyglycolic (Dexon) sutures in cataract surgery *Acta ophthal (Kbh) 57* 33–40

Sherman S E (1979) Evaluation of an improved suture for cataract surgery *Ann Ophthal 11* ?69–271

Thygesen J Reersted P Fledelius H & Corydon L (1979) Corneal astigmatism after cataract extraction *Acta ophthal (Kbh) 57* 234–251

White R H & Parks M M (1974) Polyglycolic acid sutures in ophthalmic surgery *Trans amer Acad. Ophthal Otolaryng 78* 632–636

Williamson D E (1974) The use of polyglycol c acid sutures in outpatient cataract surgery *Ann Ophthal 6* 333–340

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HISTOPATHOLOGY OF CLINICALLY SUCCESSFUL INTRAOCULAR LENS IMPLANT

BY

ULF KRAUSE and AHTI TARKKANEN

A 50 year-old man had an intracapsular cataract extraction with placement of a Worst medallion iris supported lens. After 6 days postoperatively the eye appeared quiet, the cornea was clear and the implant in place. The patient died 17 days postoperatively of subarachnoid haemorrhage. Histopathological examination revealed slight loss of endothelial cells in the upper corneal region, pressure atrophy without signs of repair of the iris stroma, loss of pigment epithelial cells of the iris in places as well as local pigment epithelial cell proliferations. The chamber angle was open and the anterior uvea revealed only a minimal inflammatory cell reaction. The unoperated opposite eye showed cortical cataract as well as advanced hypertensive retinopathy.

Key words: lens implant – histopathology – cataract extraction

In the recent surveys of intraocular lens implant surgery promising visual resu[lts] have been reported (Jaffe 1976). The clinical complications are also reflected in t[he] histopathological reports which have been compiled in the Table I. The ea[rly] reports deal with the posterior chamber implants by Ridley and the different typ[es] of anterior chamber implants. The recent reports deal with present iris support[ed] or irido-capsular type implants. As, however, we have been unable to find a[ny] report of a clinically successful implant procedure with a short observation perio[d], we thought it justified to report our observations on a clinically successful case [of] implantation of the Worst medallion lens where the patient unexpectedly died 1[7] days postoperatively.

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Table I

Some histopathological studies on eyes with intraocular lens implant

Author(s)		Postop time	Type of lens implant	Comments
heobald	1953			
ıntelen & ıubermann	1956	1 year	Posterior chamber lens of Ridley	post mortem
rancois et al	1956	1½– 25 months		
mith	1956		Ridley	
shton & Choyce	1959	6 weeks	Anterior chamber implant (Strampelli)	post mortem
ınkhorst	1959		Anterior chamber implant	post mortem
shton & ıoberg Ans	1961	½ year	Anterior chamber implant (Boberg Ans)	post mortem
ıresnick	1969		Anterior and posterior chamber implants	17 enucleated eyes 11 postmortal eyes
ıauman & Ortbauer	1970	8 years	Dannheim	post mortem
Ianschot	1974	7 weeks – 5 years	Binkhorst	2 enucleated eyes 8 postmortal eyes
affe	1976		Copeland	post mortem
Iosier et al	1977	17 weeks	Binkhorst	Fungal endophthalmitis

Material

A 50-year-old man had a kidney transplant due to chronic glomerulonephritis in 1974 The postoperative regime consisted of systemic corticosteroid and antihypertensive medication The patient noticed a decrease of vision in 1975 In 1977 he had difficulties in reading and was unable to drive a car A dense posterior cortical opacity was present in both lenses as well as signs of a hypertensive retinopathy The patient had an intracapsular cataract extraction in the left eye in August 1977 with placement of a Worst Medallion iris-supported lens A Graefe section with enlargement of the operative wound with scissors was performed. The artificial lens was implanted with some difficulty as the anterior chamber remained shallow due to vitreous bulge The operative wound was closed with 10 10-0 nylon monofilament sutures The lens was sutured to the iris with one perlon suture The anterior chamber was reformed with Balanced Salt Solution® (Alcon) During the postoperative period the lens remained in place the cornea was oedematous for six days After that the eye when observed with a hand held bio microscope was quiet the cornea clear and the lens without miotics in place The optic disc appeared engorged with retinal haemorrhages

After the first postoperative day the patient went comatose and a subarachnoidal haemorrhage due to a hypertensive crisis was diagnosed. The patient seemed to recover but suddenly 17 days postoperatively. At autopsy a rupture of the basilar artery aneurysm subarachnoid haemorrhage were diagnosed. Both eyes were obtained at autopsy

Results

Right eye

Macroscopic and microscopic examination of this unoperated eye showed co[illegible] cataract and advanced hypertensive retinopathy

Left eye

Macroscopic examination. The eye was opened through the vertical meridian showed no lens remnants. The implant was in place with no reaction around it. vitreous was clear. A few haemorrhages were observed in the retina. Haema[illegible] eosin, van Gieson, Periodic acid Schiff and iron stains were prepared

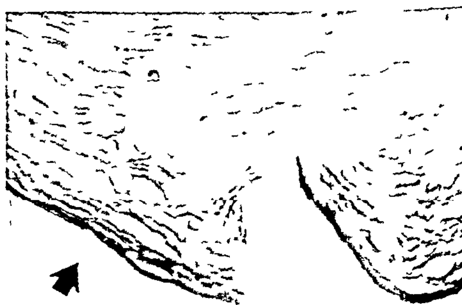


Fig 1A
The cornea shows a well healed cataract section with posterior gaping. Haematox Eosin × 50

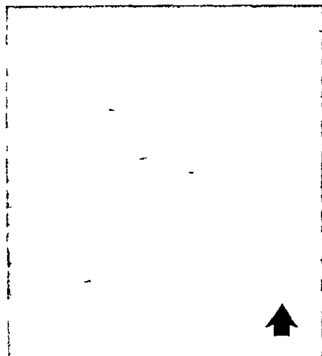


Fig 1B

ecially the central side of the corneal wound shows marked loss of endothelial cells (arrow) Haematoxylin-eosin × 100

croscopic examination A well healed corneal cataract section with some posterior ping is present (Fig 1A) The upper region of the cornea shows also some loss of dothelial cells (Figs 1A B) The chamber angle is open and the trabecular shwork is loose The iris stroma is moderately atrophic with thinning in the pillary region and stromal atrophy without signs of repair in the mid periphery gs 2 and 3) The pigment epithelial changes vary from atrophy to local oliferation and even cystic changes Only a few lymphocytes and macrophages uld be found in the iris The ciliary body shows no pathological changes

Discussion

llowing intraocular lens implantation there is rapid endothelial cell loss (Bourne Kaufman 1976) Such loss is permanent due to limited endothelial cell regenera in A loss of endothelial cells is present also in our case although clinically the



Fig 2
There is pressure atrophy of the iris in the pup llary region as well as a p gment epi he cyst Haematoxylin and eosin × 60

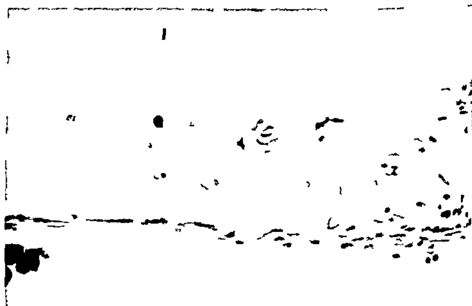


Fig 3
The iris shows marked atrophy of the stroma in the mid periphery as well as pr l ferated the pigment ep thel um Haematoxylin and eosin × 60 (i = mplant)

rnea remained clear It is due to mechanical trauma during insertion which in the esent case was made with difficulty due to vitreous bulge The pressure atrophy the iris stroma in our case confirms the observations of Manschot (1974) Its esence already 17 days after operation is however noteworthy The changes of e pigment epithelium were similar to those described by Jaffe (1976) and anschot (1974) Atrophy and proliferation due to surgical trauma and mechanical essure and friction by wire fixation loops

The atrophy is a momentary mechanical process as one is able to note marked gment dispersion during the insertion maneuver

According to Manschot (1974) of the 2724 anterior chamber lenses of the inkhorst type implanted before 1972 in the Netherlands only one eye had to be ucleated because of postoperative complications Hoffer (1978) reports the moval of 33 out of 70 000 eyes (0 05%) containing implants

In the present case the implant was well tolerated indeed In spite of the loss of ndothelial cells there were clinically no signs of corneal decompensation The iris ıanges may in part explain the reported cases of luxation or subluxation of the nplant by the erosion of the loops through the atrophic iris Still in our case the nplant was well in place As the long term results of implant surgery are uncertain Jaffe 1978) collection of clinical and histopathological data should be encouraged

References

shton N & Boberg Ans J (1961) Pathology an aphakic eye containing an anterior chamber implant. *Brit J Ophthal 45* 543–549

shton N & Choyce D P (1959) Pathological examination of a human eye containing an anterior chamber acrylic implant *Brit J Ophthal 43* 577–583

inkhorst C. D (1959) Uber die endgultige Vertraglichkeit kunstlicher Augenlinsen bei der Aphakie und deren Verbesserung mittels Fixation der Linse in der Pup lle (Pupillarl nse oder Iris Clip-Linse") *Klin Mbl Augenheilk 134* 536–543

ourne W M & Kaufman H E (1976) Endothelial damage associated with intraocular lenses *Amer J Ophthal. 81* 482–485

resnick G H (1969) Eyes containing anterior chamber acrylic implants. Pathological complications *Arch Ophthal. (Chicago) 82* 726–737

rançois J Rabaey M & Evens L (1956) Examen histo-pathologique d un oeil opere de cataracta avec inclusion d une lentille de Ridley *A n Oculist (Paris) 189* 923–931

Hoffer K J (1978) Survey on the use of intraocular lenses *Ophthalm logy 85* 400–407

affe N S (19 6) *Cataract surgery and its implications* 2nd Ed p 133 Saint Louis MO

affe N S (1978) Intraocular lenses-current status *Ophthalmology 85* 52–58

Manschot W A (1959) Bilateral cataract extraction *Ophthalmologica 137* 428–430

Manschot W A (1974) Histopathology of eyes containing Binkhorst lenses *Amer J Ophthal 77* 865–871

Mosier M A Lusk B Pettit T H Howard D H & Rhodes J (1977) Fungal endophthal mitis following intraocular lens implantation *Amer J Ophthal 83* 1–8

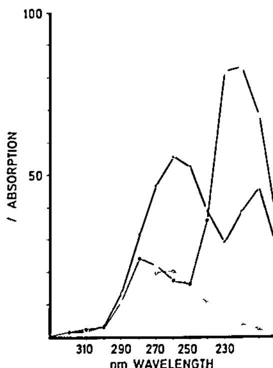


Fig 2

The curves illustrate an estimate of UV ray absorption by different potential ... substances in the cornea epithelium The ascorbic acid concentration (white ...) corresponds to the amount of the rabbit cornea epithelium whereas the protein (... circles) and the nucleic acid (triangles) correspond to the concentrations in liver cell

endothelium may be impaired during an acute attack of photophthalmia Even moderate cell loss may by recurring attacks be a factor contributing to the decompensation of the cornea This possibility should be tested in separate experiments by looking for a change in the cell number after UV ray exposure

As pointed out by Cogan & Kinsey (1946) the effects of UV radiation on the cornea is closely related to problems concerning the development of solar erythema of the skin and both of these reactions are again aspects of the general problem how radiation may influence biological activity A key role in the involved reactions is played by target molecules transforming the physical energy into biochemical processes of the tissue and a wide varity of substances (proteins nucleic acids amino acids) have been taken into consideration as potential receptors Surprisingly the AA has not been included among these components although the substance is a very labile one with high molar absorptivity (Karayannis et al 19... In order to get a rough estimation of the UV ray absorption of the AA compared

it of the proteins and the nucleic acids in the rabbit cornea epithelium all these bstances were run separately The AA content of these cells is 118 mg/100 g (Pirie 46) and since estimates of the nucleic acid concentration of the rabbit cornea ithelium apparently are lacking the present experiment was run with values om liver cells i e 10% protein and 1 1% nucleic acid (de Roberts et al 1965) Of urse it is a rough approximation when the whole intracellular protein fraction is presented by rabbit serum albumin It should also be kept in mind that the high otein synthesis of the liver cells implies that these cells are particularly rich in icleic acids This view is reflected by the observation that nucleic acids make up)% of the dry weight in the calf cornea epithelium (Zigman et al 1963) which ould mean 4 4 mg instead of 11 mg in Fig 2 when water is set to 85% of the cell hus the amount of nucleic acid used in Fig 2 represents the definite maximum lue and most probably this compound is considerably overestimated compared AA and protein In conclusion therefore it seems resaonable to include AA nong the potential receptor molecules for UV rays in the cornea epithelium when avelenghts below 290 nm are involved

Since the AA absorbs maximally around 265 nm at physiologic pH (Karayannis et 1977) it may be that the peak at 270 nm in the cornea threshold curve of Pitts 970) partly refers to this substance However the problem as to whether a omponent acts as a target substance is certainly not only a question of its molar osorptivity The absorption of light energy and its ability to harm living tissue is so supposed to depend on the local concentration of the single substance within ie cell and on the stability of the biochemical system in which it is participant.

References

achem A (1956) Ophthalmic ultraviolet action spectra *Amer J Ophthal 41* 969–975

uschke W Friedenwald J S & Moses S G (1945) Effects of ultraviolet irradiation on corneal epithelium Mitosis nuclear fragmentation post traumatic cell movements loss of tissue cohesion *J cell comp Physiol 26* 147 164

ogan D G & Kinsey V E (1946) Action spectrum of keratitis produced by ultraviolet radiation *A ch Ophthal (Chicago) 35* 670–677

e Robertis E D P Nowinski W W & Saez F A (1965) *Cell biology* p 22 4th ed W B Saunders Company Philadelphia and London

uke Elder W S & Duke Elder P M (1929) A histological study on the action of short waved light upon the eye with a note on inclusion bodies *Brit J Ophthal 13* 1–37

riedenwald J S Buschke W Crowell J & Hollaender A (1948) Effects of ultraviolet irradiation on the corneal epithelium *J cell comp Physiol 32* 161–173

Iemmingsen E A & Douglas E L (1970) Ultraviolet radiation thresholds for corneal injury in antarctic and temperate zone animals *Comp biochem Physiol 32* 593–600

arayannis M I Samios D N & Gousetis Ch P (1977) A study of the molar absorptivity of ascorbic acid at different wavelengths and pH values *Analyt chim acta 93* 275–279

Kinsey V E (1948) Spectral transmission of the eye to ultraviolet radiations *Arch Ophth (Chicago) 39* 508–513

Kurzel R B (1978) On the nature of the action spectrum for ultraviolet photokeratitis *Ophthal Res 10* 312–315

Le Grand Y (1958) La protection des yeux contre l ultraviolet *Ann oculist 191* 193–[illegible]

Martin E K (1912) The effects of ultra violet rays upon the eye *Proc roy Soc (Lond)* [illegible] 319–330

Pirie A (1946) Ascorbic acid content of cornea *Biochem J 40* 96–100

Pitts D G (1970) A comparative study of the effects of ultraviolet radiation on the eye *Am J Optom 47* 535–546

Pitts D G (1973) The ocular ultraviolet action spectrum and protection criteria *Health Phys 25* 559–566

Reim M Seidl M & Brucker K (1978) Accumulation of ascorbic acid in the corneal epithelium *Ophthal Res 10* 135–139

Scholander P F Laurence I Hemmingsen E A & Bradstreet E (1969) Ultraviolet absorption in the cornea of arctic and alpine animals In Urbach F ed *The biologic effects of ultraviolet radiation* pp 469–471 Pergamon Press

Sherashov S G (1970) Spectral sensitivity of the cornea to ultraviolet radiation *Biofizika* [illegible] 569–571

Trumpy E (1935) *Experimentelle Untersuchungen uber die Wirkung hochintensiver* Ultravioletts und Violetts zwischen 314 und 435 9 nm Wellenlange auf das Auge unter besonderer Berucksichtigung der Linse *Albrecht v Graefes Arch Ophthal 115* 495–511

Verhoeff F H & Bell L (1916) The pathological effects of radiant energy on the eye *Proc Amer Acad Arts and Sci 51* 629–759

Widmark E J (1889) Uber den Einfluss des Lichtes auf die vorderen Medien des Auges *Skand Arch Physiol 1* 264–330

Zigman S Carlsson B & Stone W Jr (1963) Nucleic acid metabolism of the corneal epithelium *Exp Eye Res 2* 217–223

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AQUEOUS HUMOUR AND ULTRAVIOLET RADIATION

BY

AMUND RINGVOLD

Studies on the ultraviolet ray absorption in the aqueous humour of rabbit cat, monkey guinea pig and rat showed marked species differences In the rabbit aqueous the ascorbic acid the proteins and some amino acids (tyrosine phenylalanine cystine and tryptophane) are together responsible for the total absorption, and a very great part of it refers to the ascorbic acid content. Accordingly species with significant amounts of ascorbic acid in the aqueous (monkey rabbit guinea pig) have a greater absorption capacity towards ultraviolet radiation than species (cat rat) lacking this substance This effect of the ascorbic acid may contribute in protecting the lens against the most biotoxic ultraviolet rays It seems that the ascorbic acid concentration is highest in the aqueous of typical day animals and lowest in species being active in the dark, indicating a correlation between the aqueous ascorbic acid level and the quantity of incident light on the eye The possible significance of changed aqueous ultraviolet ray absorption in the pathogenesis of human cataract development is discussed.

Key words eye lens – aqueous humour – cataract – ultraviolet radiation – ascorbic acid

In the past several important reports dealing with ultraviolet ray (UV ray) absorption in the light pathway of the eye have shown that radiation of potential danger for the retina is largely cut out through filtering properties of the media (Widmark 1892 Martin 1912 Verhoeff & Bell 1916 Kinsey 1948) More precisely it was found that the lens roughly absorbs rays below 400 nm wavelengh (Norren & Vos 1974) whereas the cornea and the aqueous humour remove most radiation shorter than 300 nm wavelength (Kinsey 1948 Bachem 1956 Hemmingsen & Douglas

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1970 Ringvold 1979) Accordingly the lens also has a physiologic prot against shortwave rays and it seems important to identify the different compo involved in this mechanism as well as to estimate to what extent each substance contributes to this As demonstrated in a previous analysis of the co the UV ray absorption of tissue specimens is rather complex (Ringvold 1979) situation turned out to be much simpler in the aqueous humour and this w described in the present paper

Material and Methods

Different species were used in this study 6 rabbits (5 albino 1 black) 5 domes c monkeys (cercopithecus aethiops) 10 albino guinea pigs (250–300 g) and 18 albin (150–200 g) Apart from the cats which were adult individuals of unknown age the were young adult individuals The guinea pigs received 1 mg ascorbic acid (AA) per ml to the water and the monkeys had a fruit consumption of one orange daily where other animals received no additional AA supplies beyond that contained in their n

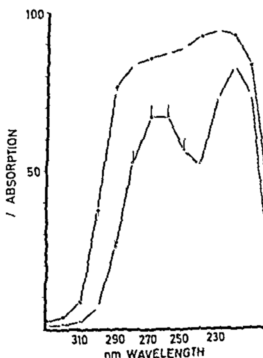


Fig 1

Absorption of ultraviolet radiation in aqueous humour from rabbit (bl k circles) a (white circles) Each curve represents mean values from 6 eyes and as seen in many ins the standard deviation does not exceed the marking pt

od Apart from the rats which were anaesthetized with ether all animals were given ntobarbitone sodium intravenously (rabbits monkeys) or intraperitoneally (cats guinea gs) In addition the monkeys were initially given 20 mg phencyclidine hydrochloride ernylan Park Davis) intramuscularly Blood and aqueous humour were rapidly aspirated om the left ventricle and the peripheral part of the anterior chamber respectively In bbits cats and monkeys the investigations were carried out on specimens from each single imal whereby aqueous from both eyes was collected as one volume In order to obtain dequate volumes from guinea pigs and rats each specimen of blood and aqueous presented a collection from several animals two groups each of 5 guinea pigs and two roups of 8/10 rats were investigated After aspiration the AA content of both serum and queous was estimated by the method of Michaelsson & Michaelsson (1967) The aqueous pecimens were tested by adding 50 µl to 950 µl serum both for sample and blank whereafter ie procedure for serum analysis was followed All investigations were run immediately after ie samples had been aspirated The spectrophotometric studies were performed with a eckman DB G instrument using quartz cells with 2 mm light pathway and the specimens ere all compared to distilled water After spectrophotometry of the aspirated aqueous and

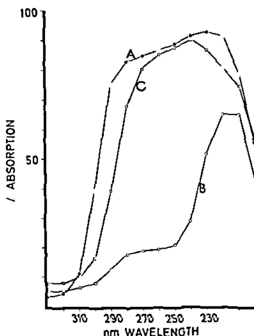


Fig 2

(Rabbit) Curve A Absorption of ultraviolet radiation through aspirated aqueous humour from one animal Curve B Same sample after dialysis against distilled water Curve C Same sample after a second dialysis against distilled water containing 25 mg AA/100 ml which was the aqueous level of this particular animal Note the excessi e AA concentration contributes considerably from the 240 nm limit towards higher wavelengths in raising the curve

subsequent determination of its AA concentration the single specimens were dialysed … 2 l distilled water at +4 C overnight while continuously stirring to eliminate the … molecular components such as AA and amino acids Spectrophotometry of these … show the UV ray absorption refering to non-dialysble components of the aqueous … protein) In order to estimate the amount of UV ray absorption by the different dialy… components the non dialysable fraction was again dialysed against the initial AA con… tion as a 2 l distilled water solution at room temperature for 4 h The difference of the … from aspirated aqueous and the spectrophotometry curve of the bag after this proce… illustrates the non AA part of the dialysable aqueous components This set up has been … for all samples but since rats did not concentrate AA into the aqueous at all a second di… of these specimens was not carried out

An artificial aqueous humour was made by mixing the following components in d… water The AA concentration was taken as in Fig 2 (25 mg/100 ml) Total protein (accor… to Neufeld et al 1972) was added as rabbit albumin (65 mg/100 ml) which in this conne… represents the different protein fractions of normal aqueous The amino acids (tyrosine … mg/l phenylalanine 20 mg/l cystine 7 mg/l tryptophane 5 mg/l) are amoun… accordance to previous findings in rabbit (Reddy et al 1961)

Chemicals l ascorbic acid l cystine l phenylalanine l tryptophane l tyrosine were Sigma products In addition crystallized rabbit albumin (Armour) was used

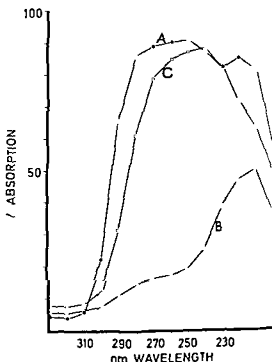


Fig 3

(Monkey) Curve A Absorption of ultraviolet radiation through aqueous humour from … animal Curve B Same sample after dialysis against distilled water Curve C Same sam… *after a second dialysis against distilled water containing 18 8 mg AA 100 ml wh…* aqueous level of this particular animal

Results

The UV ray absorption of the aspirated aqueous from 3 rabbits and 3 cats is shown in Fig 1 (Spectrophotometric studies of the cornea from the same animals have been published elsewhere Ringvold 1979)

Figs 2–6 show the UV ray absorption of different components present in the aqueous humour of rabbit monkey guinea pig cat and rat respectively Curve A represents spectrophotomety of aspirated aqueous Curve B illustrates how much the proteins contribute to the total aqueous absorption The difference between curve C and each of the curves B and A visualises the UV ray absorption of the AA respectively the non AA part of the dialysable components The difference between the curves A and C is certainly too high since the samples were too small for pH adjustment before running curve C (see below) For some unknown reason curve C is higher than the curve for aspirated aqueous above 300 mn and this phenomenon is more pronounced in the cat than in the other species

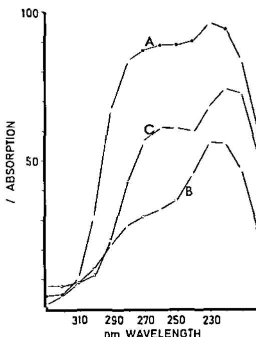


Fig 4

(Guinea pig) Curve A Absorption of ultraviolet radiation through aspirated aqueous humour collected from 5 animals Curve B Same sample after dialysis against distilled water Curve C Same sample after a second dialysis against distilled water containing 9 6 mg AA/100 ml which was the aqueous level of this specimen



Fig 5

(Cat) Curve A Absorption of ultraviolet radiation through aspirated aqueous h collected from one animal Curve B Same sample after dialysis against distilled water C Same sample after a second dialysis against distilled water containing 1 ? mg AA I which was the aqueous level of this particular animal

In Fig 7 it is tried to imitate UV ray absorption of the aspirated rabbit aque mixing an artificial aqueous described under Material and Methods *It is seen* after adjustment to pH 7 0 with 0 1 M sodium bicarbonate the UV ray absor of this artificial aqueous roughly corresponds to that of the aspirated specimen

In order to obtain the total in vivo UV ray absorption of the rabbit an aqueous the curves from Fig 1 are in Fig 8 adjusted to the real light pa length through the anterior chamber of 3 5 and 4 5 mm respectively Discussion for furher comments on this graph

The AA content for the aqueous humour from the different species expres *mean ± SD (mg/100 ml) were rabbit 23 5 (3 0) monkey 17 0 (? 5) guinea p* (4 2) cat 1 5 (0 4) rat 0 6 (0 5)

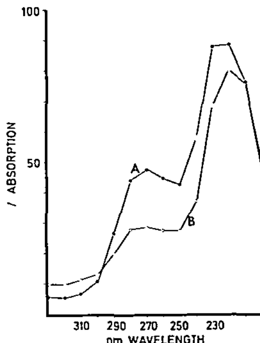


Fig 6

Rat) Curve A Absorption of ultraviolet radiation through aspirated aqueous humour collected from 10 animals Curve B Same sample after dialysis against distilled water

Discussion

From this study it can be concluded that the rabbit aqueous humour does not contain any components contributing significantly in its UV ray absorption beyond AA serum protein and some amino acids Conditions are probably similar in monkey and guinea pig in contrast to the aqueous of cat and rat in which the AA concentration is practically zero Of particular interest is the considerable absorption of UV radiation by the AA which has also been mentioned by Balazs (1954)

In view of the increasing evidence that UV radiation may cause cataract (Duke Elder 1926 Pirie 1968 Heyningen 1973 Kurzel & Wolbarsht 1973 Zigman et al 1973 Weiter & Finch 1975 Borkman & Lerman 1977 Hiller et al 1977) it is imporant to know that only wavelengths down to about 290 nm penetrate to earth (Robinson 1966) Furthermore since light energy is inverse to its wavelength the rays just above the 290 nm limit are likely to be the most biotoxic of the solar spectrum It has previously been shown that as much as 20% of this radiation penetrates the rabbit cornea and the percentage is even higher in other species

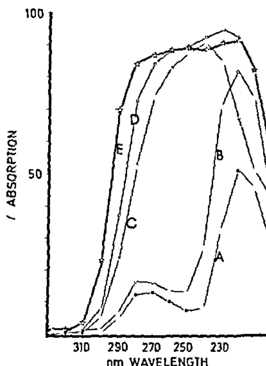


Fig 7

Absorption of ultraviolet radiation through an artificial aqueous humour (curve E) Curves A B and C show the absorption of distilled water containing amino acid protein and ascorbic acid respectively Curve D represents the components from A B and C as one sample showing pH 3 7 Curve F shows the solution from curve D after adjustement of pH 7 0 Broken line illustrates aspirated rabbit aqueous absorption from Fig [illegible] for comparison

(Ringvold 1979) The fate of UV radiation penetrating the cornea central depends on the absorption properties behind this level i e in the first place on the absorbing capacity of the aqueous humour In Fig 8 this capacity is shown for the rabbit eye which is used as experimental model Interestingly Bachem ([illegible]) reported that the UV action spectrum for the development of rabbit cataract is very characteristic "This representative curve begins abruptly between 293 and [illegible] reaches its peak near 297 nm falls rather abruptly to 313 nm and has a long [illegible] through the near ultraviolet" These observations are confirmed by Pitts et al (1977) which are interposed in Fig 8 From this figure it is seen that the cataractogenic effect steeply increases from 310 to 300 nm although the corneal transparency decreases in the same interval From 300 to 290 nm however the the decrease in transparency levels off the expected further increase in the cataract curve is exchanged with an abrupt fall towards zero It seems likely to connect the

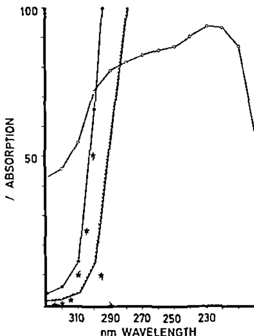


Fig 8

he absorption curves for aqueous humour from Fig 1 are adjusted to anterior chamber ·pth of 3 5 mm for the rabbit (black circles) and 4 5 mm for the cat (double line) Pitts diant exposure threshold data for the action spectrum producing cataracts are shown roken line with stars) The maximum value of this curve which corresponds to the lowest reshold value is arbitrarily set to the 50% level The absorption curve of the rabbit cornea (Ringvold 1979) has open circles

renomenon with the UV ray absorption in the aquous humour which accord ıgly in the rabbit to some degree acts as a fluid UV filter protecting the lens As ıown in this study this effect of the rabbit aqueous largely refers to its high AA ›ncentration

The rabbit eye may also be an adequate model to estimate the possible ıgnificance of the aqueous AA level in the pathogenesis of human cataract since ıe anterior chamber depth is 3 5 mm both in rabbit (Tripathi 1974) and man Rosengren 1950) and the aqueous AA level is roughly of the same order in both ›ecies It is evident from Fig 8 that a decrease in AA concentration of the aqueous ıeans a lower slope of its absorption curve which opens for the most biotoxic ıdiation to the lens One interesting question is therefore whether the AA level in ıqueous in cataractous eyes is reduced or not In fact several authors report that ıis is the case (Muller & Buschke 1934 Nakamura 1935 Gala & Melka 1936

Purcell et al 1954) although not all reports are in keeping with this con (de Bernardinis et al 1965) It should be reminded that the AA concentra both the aqueous (Kinsey 1947) and the cornea (Reim et al 1978) depends plasma level and from figure 2 in Kinsey (1947) it is seen that even small cha the plasma content induces large fluctuations in the aqueous level Since the a plasma AA level is reduced about 50% in geriatric subjects (Loh & Wilson 19 the protection of the lens against UV radiation is suggested to decrease increasing age Thus keeping in mind that cataract development probably cumulative effect over years it seems that reduced AA concentration in the aque humour either because of low serum level or because of defect concentra mechanism in the ciliary body may be a factor of significant pathophysiolo importance As Muller & Buschke (1934) came to the same conclusion, t assumed that AA is necessary in the lens metabolism to maintain transparency contrast to their view the here presented "optical funct on" of AA is based on high molar absorptivity of this substance

According to the present study there are marked species differences in lens protecting capacity of the aqueous Thus both in the cat and the ra absorption is rather low through the 2 mm thick aqueous sample The cat howe has a light pathway through the anterior chamber of as much as 4.5 mm (Trp 1974) and the total absorption is therefore significant *in vivo* despite extremely AA values (see Fig 8) It is evident that despite the deeper anterior chamber cat (4 5 mm) compared to the rabbit (3 5 mm) the cat s lens has the lower degr UV protection of the two above 290 nm largely due to the lower AA level in aqueous As a night animal the cat perhaps has no need of this protection (aspect speaking in favour of this view may been seen in Table I indicating a gen trend relating aqueous AA level of the different species to the quantity of avail light Accordingly typical day animals are found at the top of the table with h values whereas night animals are at the bottom In between there are species dog and pig whose predecessors (jackal wild boar) in part are operating during day break It is of particular interest that the primates owl monkey and galago (monkey) which both operate in the dark have low AA values in the aqueous contrast to day monkeys (macaca and cercopithecus)

The common feature of all structures interposed between the body surface a the sensory cells of the eye is to mediate light onto the receptors and all along pathway light energy is absorbed in different tissues before photons are tra formed to nerve impulses in the outer segments Since free radicals and unpa electrons are generated wherever molecules are broken up by some energ process such as e g attack of light energy (Commoner et al 1954 1957 Herfeld Bass 1957 Pathak & Stratton 1969 Lukiewicz 1972) it is reasonable to assume substantial amounts of such components are continuously formed in the eye and

Table [illegible]

...orbic acid concentration (mg/100 ml) in the aqueous humour [illegible] ...ble is largely based on Davson ([illegible]) Table [illegible] ...ded

Species	Aqueous humour	Authors
Rabbit	[illegible]	[illegible]
(w[illegible])	110	[illegible]
	33	[illegible]
	[illegible]	[illegible]
Ox	[illegible]	[illegible]
	10	[illegible]
	110	[illegible]
	10	[illegible]
Horse	10	[illegible]
	110	[illegible]
	10	[illegible]
	18[illegible]	[illegible]
Man	13 0	[illegible]
	12 [illegible]	[illegible]
Monkey (macacus [illegible])	[illegible]	[illegible]
(cercopithecus [illegible])	17 0	[illegible]
Guinea pig	22 0	[illegible]
	21 0	[illegible]
	[illegible]	[illegible]
	[illegible]	[illegible]
Sheep	[illegible]	[illegible]
	17 0	[illegible]
Pig	[illegible]	[illegible]
	[illegible]	[illegible]
Woodchuck	[illegible]	[illegible]
Dog	[illegible]	[illegible]
	[illegible]	[illegible]
Owl monkey	[illegible]	[illegible]
Dogfish	[illegible]	[illegible]
Cat	[illegible]	[illegible]
	[illegible]	[illegible]
Frog	[illegible]	[illegible]
Great horned [illegible]	[illegible]	[illegible]
Galago bush baby	[illegible]	[illegible]
Rat	[illegible]	[illegible]
	[illegible]	[illegible]

As in the skin (Daniels 1959) the generation of that highly reactive and ine fragments in eye tissues calls for a protective mechanism The AA has prev been designated the role as participant in an electron transport system (II 1962) but so far a metabolic reaction for which that excessive transport cap would be necessary in the eye has not been found It is tempting to su therefore that the reversible redox reaction between AA and dehydro-AA m involved in taking care of radiation induced free radicals in the eye media (co lens retina) in general

References

Bachem A (1956) Ophthalmic ultraviolet action spectra *Amer J Ophthal 41* 969–9 5

Balazs E A (1954) Studies on the structure of the vitreous body I The absorption ultraviolet light *Amer J Ophthal 38* 21–28

Balazs E A Laurent T C Laurent U B G DeRoche M H & Bunney D M (1959) S on the structure of the vitreous body VIII Comparative biochemistry *Arch b biophys 81* 464–479

de Berardinis E Tieri O Polzella A & Iuglio N (1965) The chemical composition of hum in aqueous humour in normal and pathological conditions *Exp Eye Res 4* 1 9 ?

Bito L Z & Roberts J C (1974) The effects of hibernation on the chemical compositi cerebrospinal and intraocular fluids blood plasma and brain tissue of the woodc (marmota monax) *Comp biochem physiol 47* 173–193

Borkman R F & Lerman S (1977) Evidence for a free radical mechanism in agin u v irradiated ocular lenses *Exp Eye Res 25* 303–309

Commoner B Townsend J & Pake C E (1954) Free radicals in biological materials *N 174* 689–691

Commoner B Heise J J Lippincott B B Norberg R F Passonneau J V & Townsen (1957) Biological activity of free radicals *Science 126* 57–63

Daniels F (1959) The physiological effects of sunlight *J invest Dr 32* 147–155

Davson H (1956) *Physiology of the ocular and cerebrospinal fluid* p 9 J & A Church London

Davson H & Luck C P (1959) Chemistry and rate of turnover of the ocular fluids of bush baby (galago crassicaudatus agisymbanus) *J Phys iol (Lond) 145* 433–459

Doolittle R F Thomas C & Stone W Jr (1960) Osmotic pressure and aqueous hum formation in dogfish *Science 132* 36–37

Duke Elder W S (1926) The pathological action of light upon the eye Part II Action o the lens Theory of the genesis of cataract *Lancet I* 1188–1191

Gala A & Melka J (1936) Der Gehalt an Vitamin C im Humor a q eus des normalen pathologisch veranderten Auges *Arch Augenheilk 109* 726–736

Heath H (1962) The distribution and possible functions of ascorbic acid in the eye *Ex res 1* 362–367

Hemmingsen E A & Douglas E L (1970) Ultraviolet radiation thresholds for corneal in antarctic and temperate zone animals *Comp biochem phy iol 32* 593 600

Hertzel J C M & Bass A M (1957) Frozen free radicals *Sci Amer 196* 11–107

Heyningen R. (1973) Assay of fluorescent glucosides in the human lens Exp Eye Res 15
?1–126
er R Giacometti L & Yuen K (1977) Sunlight and cataract An epidemiologic
vestigation Amer J Epidem 105 450–459
nson S W (1936) Cataract and ascorbic acid in the guinea pig eye B ochem. J 30
130–1437
sey E V (1947) Transfer of ascorbic acid and related compounds across the blood
queous barrier Amer J Ophthal 30 1262–1266
sey E V (1948) Spectral transmission of the eye to ultraviolet radiations A ch Ophthal
Chicago) 39 508–513
sey E V & Jackson B (1949) Investigation of the blood aqueous barrier in the newborn
mer J Ophthal 32 374–378
zel R B & Wolbarsht M L (1973) Spectral studies on normal and cataractous intact
uman lenses Exp Eye Res 17 65–71
gham M (1950) The transfer of l ascorbic acid and dehydro-l ascorbic acid into the
queous humour of the rabbit and cat J Physiol (Lond) 111 388–393
H S & Wilson C W M (1971) Relationship between leucocyte and plasma ascorbic acid
oncentrations Brit med J 3 733–735
stewicz S (1972) The biological role of melanin I New concepts and methodical
pproaches Folia histochem cytochem 10 93–107
rtin E K (1912) The effects of ultra violet rays upon the eye Proc roy Soc (London) 85
19–330
haelsson G & Michaelsson M (1967) A new diazo method for the determination of
scorbic acid in blood plasma Scand J clin lab Invest 20 97–103
ller H K & Buschke W (1934) Vitamin C in Linse Kammerwasser und Blut bei
ormalem und pathologischem Linsenstoffwechsel Arch Augenheilk 108 368–390
kamura B & Nakamura O (1935) Uber das Vitamin C in der Linse und dem Kammer
wasser der menschlichen Katarakte Albr Graefes Arch Ophthal 134 197–200
ufeld A H Jampol L M & Sears M L (1972) Aspirin prevents the disruption of the
lood aqueous barrier in the rabbit eye Nature 238 158–159
rren D V & Vos J J (1974) Spectral transmission of the human ocular media Vis Res 14
1237–1244
hak M A & Stratton K (1969) Effects of ultraviolet and visible radiation and the
production of free radicals in skin In Urbach F ed The biologic effects of ultraviolet
radiation pp 207–222 Pergamon Press
ie A (1968) Color and solubility of the proteins of human cataracts Invest Ophthal 7
534–550
ts D G Harker P D & Parr W H (1977) Ocular ultraviolet effects from 295 nm to 400
nm in the rabbit eye NIOSH research report publication No 77–175 p 75 U S
Department of Health Education and Welfare
desta H H & Baucke J (1938) Woher kommt das Vitamin C in den verschiedenen
Geweben des Auges? Albrecht v Graefes Arch Ophthal 139 720–731
rcell E F Lerner L H & Kinsey E V (1954) Ascorbic acid in aqueous humour and serum
of patients with and without cataract. Arch Ophthal (Chicago) 51 1–6
ddy D V N Rosenberg C & Kinsey E V (1961) Steady state distribution of free amino
acids in the aqueous humours vitreous body and plasma of the rabbit. Exp Eye Res 1
175–181

Reim M Seidl M & Brucker K (1978) Accumulation of ascorbic acid in the ... epithelium *Ophthal Res 10* 135–139

Ringvold A (1979) Cornea and ultraviolet radiation *Acta ophthal (Kbh) 57* 63–68

Robinson N (1966) *Solar radiation* Elsevier Publishing Company Amsterdam London New York

Rosengren B (1950) Studies in depth of the anterior chamber *Arch Ophthal (Chic)* ... 523–538

Tripathi R C (1974) Comparative physiology and anatomy of the aqueous outflow pa... In Davson H and Graham L T Jr ed *The eye* vol 5 Comparative physiology p... Academic Press New York and London

Verhoeff F H & Bell L (1916) The pathological effects of radiant energy on the eye *Pr amer Acad Arts and Sci 51* 629–759

Vladesco R & Stefanesco H (1939) Teneur en acide ascorbique des yeux chez differ... especes animales C r Seanc *Soc Biol 132* 169–171

Weiter J J & Finch E D (1975) Paramagnetic species in cataractous human lenses *Na... 254* 536–537

Widmark J (1892) Über die Durchdringlichkeit der Augenmedien fur ultraviolette Str... *Skand Arch Physiol 3* 14–46

Zigman S Schultz J & Yulo T (1973) Possible roles of near UV light in the catara... process *Exp Eye Res 15* 201–208

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CLINICAL EXPERIENCE WITH CONTINUOUS WEAR HYDROPHILIC CONTACT LENSES IN APHAKIA

BY

S BARNER K MARNER and J A FAHMY

Twenty two aphakic eyes in seven females and thirteen males were fitted with a new type of soft contact lens designed for continuous wear Nine patients were operated on for unilateral traumatic cataract and eleven patients were operated on for senile cataract Sixteen patients terminated the study In all cases the visual acuity with lens was almost equal to the acuity obtained with spectacles The lenses were well tolerated without any special wearing schedule No serious complications occurred However about one third of the patients developed conjunctivitis during the investigation period of eleven months Four patients showed mild limbal vascular reaction while only one patient had neovascularisation along the corneal scar caused by the original trauma The new lens was found to be a good alternative to other contact lenses

Key words contact lenses – cataract – aphakia – infections

With the introduction of hydrated polymethylmethacrylate in the production of soft contact lenses by Wichterle & Lim (1960) a new era in this field was established Since then many materials with several improvements have been presented

The latest development seems to be materials designed for extended "permanent wear The initial success of continuous wear depends almost entirely on the oxygen permeability of the material (Fatt & St Helen 1971 Leibowitz et al 1973 Fatt & Morris 1977) Most of the lenses used in previous clinical trials (Shaw & Gasset 1973 Jackson & Aquavella 1976 Pierse & Kersley 1976 Gasset et al 1977 Binder & Worthen 1977) were co-polymers of hydroxyethylmetacrylate (HEMA)

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or polymethylmethacrylate (PMMA) with polyvinylpyrolidone (PVP) or ethyle glycoldimethacrylate (EDMA) which provide low to moderate oxygen permeab (Ruben 1978)

The purpose of this investigation was to evaluate the clinical results of a newly material (Duragel 75) with different physical and chemical properties The mate used is a complex multicomponent cross linked amido-amino co-polymer basically hydrophobic nature to which hydrophilic sites are grafted and it is q unrelated to HEMA and derivative systems (Frankland & Highgate 1977 Rub 1978) The data of the lens used in the present study are shown in Table I

Material and Methods

The material comprises 20 patients (22 eyes) admitted to the Eye Departme Kommunehospitalet Copenhagen from August 1977 to July 1978 for catar surgery Nine patients were operated on for unilateral traumatic cataract, an eleven patients were operated on for senile cataract Two patients in the L group were operated on both eyes

During the trial period all patients who underwent surgery for traumat cataract were offered to participate in the study whereas patients in the seni group were selected in regard to cooperation and motivation Patients w persistent corneal astigmatism exceeding 2 diopters were not included The a and sex distribution appear from Table II

The mean interval between operation and contact lens fitting was 1? wee (range 6 26) in the traumatic group and 9 weeks (range 4 19) in the senile group

Table I

Contact lens specifications

Name	Scanlens 24 H
Material	Amido-amino copolymer
Water content	76% (?0°C)
Oxygen permeability	40.0×10^{-11} units*
Optical transmission	97%
Refractive index	1 379
Centre thickness	0 4 – 0,5 mm
Base curves	7 9 – 8 1 – 8 3 – 8 5 mm
Diameter	13,5 mm

* units ($cm^2 \times ml\ O_2/sec \times ml \times mmHg$)

Table II
Age and sex distribution

Age	Traumatic		Senile		Total
	Male	Female	Male	Female	
<10	1	1			2
11–20	2				2
21–50	5				5
51–60			2	3	5
>60			3	3	6
Total	8	1	5	6	20

To avoid decentration fitting was performed steeper than recommended by the manufacturer (0 5 mm flatter than mean "K" reading) and was usually around the flattest K" reading After initial fitting the patients were examined with the slitlamp after one h 24 h one week and monthly or more often when necessary

The patients were instructed not to remove the lens at any time and to contact the clinic in case of pain discomfort or redness of the eye The lenses were cleaned and boiled individually but mainly in the presence of discomfort and/or deposits

Results

Twenty patients (22 eyes) were eligible according to the criteria described in methods One patient was not included because of problems with the supply of an adequate lens Nineteen patients were evaluable and with the exception of 3 patients were wearing the lenses throughout the period of investigation These 3 patients were terminated before schedule because of recurrent deposits fitting problems with resulting lens displacement and irritation of the eye Thus 16 patients (18 eyes) were wearing appropriate lenses at the termination of the study

Wearing period shown in Fig 1 is the cumulative data for all lenses used in the different patients corrected for short interruptions these interruptions represent 52 days in 6 patients and wearing period and observation period are then almost equal Interruptions were caused by infectious conjunctivitis (30 days in 4 eyes) and by loss of lenses cleaning and operation of the fellow eye (22 days in 3 eyes) The wearing period varied from one to eleven months About 50% of the eyes had been wearing the lenses for more than six months at the termination of the investigation

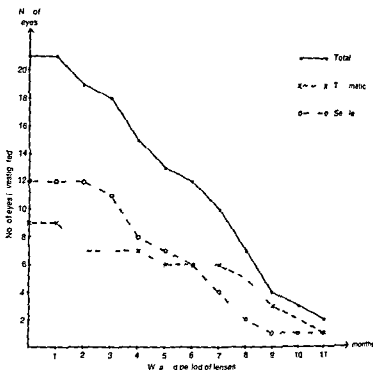


Fig 1

Wearing periods in months (the data are corrected for short interruptions specified in the text)

Visual acuity was significantly the same when comparison was made between contact lenses and spectacles Thus in 15 eyes the visual acuity was equal while in 6 eyes belonging to the traumatic group spectacles were slightly superior in 3 cases and contact lenses slightly better in 3 other cases

Table III

Causes of replaced lenses

Causes of replaced lenses	Traumatic	Senile	Total
Lost lenses	1	2	3
Broken lenses	1	1	2
Deposits	4	6	10
Fitting process	8	4	12
Total	14	13	27

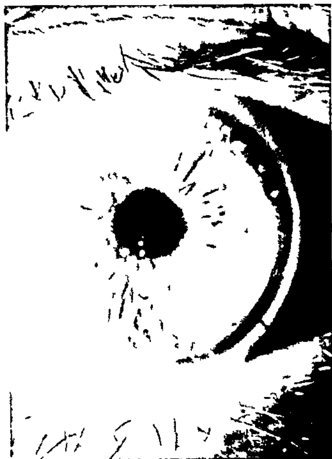


Fig 2
Depos ts on the surface of a lens

Replacement of lenses was done when necessary due to the causes listed in Table III The relatively high number of lenses replaced in the fitting process was due to echnical problems with the new type of lenses Ten lenses were replaced due to leposits which was one of the most annoying problems The table shows deposits to e responsible for replacement in about 2/3 of definite lenses and in 1/3 of all eplacements The deposits were round glossy whitish and prominent (Fig 3) The umber ranged from one single large deposit to countless smaller spots The lurability of the lenses varied from 2 weeks to 10 months (average 5 months)

omplications from the wearing of the lenses were mainly of infectious and vascular ature Infectious conjunctivitis was seen in 7 eyes (6 patients) all treated success

fully with antibiotics and 4 eyes (3 patients) had concomitant interruption of t wearing Vascular reactions were found in five eyes only one in the form neovascularisation but this could have been caused by the perforating trauma the proliferation was seen in relation to the scar Other vascular reactions (4 e appeared as moderate dilatation of the perilimbal vessels after 70–120 days permanent wearing of the lens No corneal or intraocular infections were seen any of the eyes

Discussion

The present results have demonstrated that the examined lens seems to be a g alternative to the other various types of contact lenses for the correction unilateral aphakia

From the practitioner s point of view the lens was relatively easy to fit, because its large diameter and few curves (only 4 alternatives)

The lens was well tolerated without any special wearing schedule Sixteen of patients terminated the study which may be regarded as a high rate of wear success The visual acuity with the lens was as good as the acuity obtained w spectacles which may indicate good optical properties

Some shortcomings deserve attention First the relatively short durability of t lenses which varied in average from 3 to 5 months Second the relatively h frequency of deposits which were resistant to cleaning aids and were of g annoyance to the patients as well as to the practitioner The relatively high numb of control visits was considered another disadvantage

There have been no serious complications in the present study such as corn ulcers or intraocular infection as reported by some other authors (Kersley e 1977 Cooper & Constable 1977) However nearly one third of the patients h infectious conjunctivitis which is in accordance with other reports dealing w continuous contact lens wear (Benson 1976 Gasset 1977) This fact may demo strate the necessity of a careful instruction of patients to contact their ophthalmo gist immediately in the case of pain redness of the eye or haziness of sight

References

Benson C (1976) Continuous use of contact lenses *Austr J Ophthal* 4 99–103

Binder P S & Worthen D M (1977) Clinical evaluation of continuous wear hydrop lenses *Amer J Ophthal* 83 549–553

Cooper R L & Constable I J (1977) Infective keratitis in soft contact lenses wearers Br *ophthal* 61 250–254

Ellis P (1977) The use of permanent wear contact lenses in young aphakic children Co *Lens J* 5 23–26

t I & St Helen R (1971) Oxygen tension under an oxygen permeable contact lens *Amer Optom 48* 545–555
t I & Morris J (1977) Oxygen transmissibility changes of gel contact lenses during wear *The optican 174* 17–20
inkland J D & Highgate D J (1977) *Practioners fitting guide* Duralens Ltd.
sset A R Lobo L & Houde W (1977) Permanent wear of soft contact lenses in aphakic yes *Amer J Ophthal 83* 115–120
kson G K & Aquavella J V (1976) Clinical experience with hydrophilic lenses in monocular aphakia *Ann Ophthal 8* 156 163
rsley H J (1977) The use of a "continuous wear hydrophilic lens in aphakia *Contact Lens 5* 13–16
rsley H J Kerr C & Pierse D (1977) Hydrophilic lenses for continuous-wear in aphakia Definitive fitting and the problems that occur *Brit J Ophthal 61* 38–42
rsley H J (1977) Soft contact lenses in aphakia *Contact Lens J 5* 29–30
ibowitz H M Laing R A & Sandstrom M C (1973) Continuous wear of hydrophilic contact lenses *Arch Ophthal (Chicago) 89* 306–310
rse D & Kersley H J (1976) Fitting continuous-wear" soft contact lenses at the time of cataract extraction *Trans ophthal Soc U K 96* 11–12
rse D & Kersley H J (1977) Hydrophilic lenses for continuous-wear in aphakia Fitting at operation *Brit J Ophthal 61* 34–37
iben M (1978) A clinical appraisal of a 75% hydrophilic soft lens *J Brit Contact Lens Assoc 1* 3
aw E L & Gasset A R (1973) Experience in the use of soft contact lenses for the correction of monocular and binocular aphakia *Ann Ophthal 5* 937–943
ichterle O & Lim D (1960) Hydrophilic gels for biological use *Nature 185* 117–119

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SOFT CONTACT LENSES WORN AT A SIMULATED ALTITUDE OF 18 000 FEET

BY

RUNE HAPNES

Five subjects wearing soft contact lenses were placed in a low pressure chamber where the atmospheric pressure was reduced to 50%. Subjective and objective criteria were used to determine corneal distress. After four hours at ½ atmosphere all 10 eyes showed objective changes and four out of five subjects claimed subjective changes indicating corneal distress. None of the subjects showed subjective or objective signs of similar changes when the study was repeated at normal atmospheric pressure.

Key words: soft contact lenses – high altitude – corneal distress – corneal epithelial hypoxia

Like all other cells in the body, the corneal epithelial cells need oxygen to maintain normal function. In contrast to most other cells, they do not get their oxygen from the blood, but directly from the surrounding area through the pre-corneal tear film (Smelser & Ozanics 1952). In an open eye the partial oxygen tension in the tear film is roughly equal to the atmospheric oxygen tension, that is about 155 mmHg. When the eyelids are kept closed the partial oxygen tension is reduced until it is in equilibrium with the oxygen tension in the palpebral capillaries – about 55 mmHg (Fatt & Bieber 1968). This is more than adequate to maintain normal corneal function.

When a contact lens is placed on the cornea, the pre-corneal oxygen tension is reduced by an unknown quantity. If the lens is too big, too tightly fitted or, in the case of oxygen permeable lenses, too thick, symptoms of corneal hypoxia may occur. It has been estimated that the corneal epithelium needs a minimal oxygen

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nsion of 11 to 19 mmHg to function normally over a longer period of time (Polse Mandell 1970)

A fully oxygenated cornea has oxygen reserves for about two hours continued ormal function if all further oxygen supplies are prohibited (Uniacke et al 1971)

Most of the contact lenses in common use today are aimed at being worn only for limited period of time usually not exceeding normal waking hours One such ns type is the HEMA lens

Patients with these lenses can wear them throughout the day without experi ncing any discomfort but most of them will rapidly develop symptoms of verwear (= corneal hypoxia) if they fall asleep with their lenses on It follows that a re lens oxygen tension of 155 mm is enough to supply adequate oxygen to the ornea but a pre lens oxygen tension of only 55 mm is *not* sufficient It has also een reported that patients with lenses that are fitted and functioning well at sea vel can have problems at high altitudes where the oxygen tension is lower (Clarke 976) This article aims at studying the effects of high altitude on lens covered orneas

Materials and Methods

he study was performed in the low pressure chamber of the Norwegian Institute f Flight Medicine In this chamber it is possible to control the atmospheric pressure nd thereby the partial oxygen tension the temperature the air circulation and entilation light conditions and to some extent also relative humidity Five people earing well fitted soft contact lenses (HEMA lenses) on both eyes were selected for his experiment They were aged from 20 to 40 years four females and one male hey all had uncomplicated myopias ranging from −1 5 to −7 with corrected ision ranging from 6/5 to 6/8 5

In the chamber the following parameters of corneal distress were recorded

Subjective changes (fogging of vision and discomfort)

Changes observed with slit lamp (sclerotic scatter ciliary injection debris orneal thickness changes)

3 Changes in visual acuity (with standard contrast and low contrast)

The five test persons and the examiner were fitted with tight fitting oxygen masks naintaining an oxygen supply equal to 155 mmHg

When the above criteria of the cornea had been checked at normal atmospheric pressure the pressure inside the tank was fairly rapidly reduced by half (simulating n altitude of 18 000 feet) The partial oxygen tension was just under 80 mmHg The temperature the humidity and the light conditions were kept constant during

Table I
Physical conditions in the chamber

Temperature	21 C
Relative humidity	11–13%
Chart illumination	35 lux
Draught	Negligible
Atmospheric pressure	¹ atm ,ß 80 mm
Atmospheric pressure control	1 atm ,ß 126 mm

the experiment The air circulation varied slightly but was kept well below the normally termed draught conditions The contact lenses were kept on at all times during the experiment also during the recovery period after descent to normal atmospheric conditions Slit lamp examination was performed with a Haag Streit slit lamp fitted with a Maurice Guardini pachometer giving an accuracy measurement ± 0 015 mm (3%) The cornea was examined first with a fine slit, then with sclerally scattered light the limbus area was examined for injection and the tear menisc was examined for debris Visual acuity was first tested with a standard Monoyer chart and then with a low contrast visual chart made of ordinary Snellen letters reflecting 80% of on falling light on a background reflecting 88% of on falling light

Results

During the first two hours of the experiment no subjective or objective changes were observed After about two hours three of the test patients developed debris in the tearfilm in both eyes most easily observed in the tear menisc at the upper margin of the lower lid One of the test persons started to complain of slight corneal irritation at about this time After three hours debris was observed in all ten eyes After three hours three of the five persons experienced irritation in both eyes and after four hours one of the test persons was so uncomfortable that we had to interrupt the experiment She had then rather pronounced ciliary injection in both eyes There was photophobia and abundant lacrimation

No changes in the corneal thickness were registered during the experiment.

The visual acuity was reduced by one to three lines on the Monoyer chart in six out of ten eyes It was unchanged in four eyes The visual acuity on the special low contrast chart was reduced by one line or more in four eyes and was unchanged in six eyes (One of the test persons who had unchanged visual acuity on the Monoyer chart had rather pronounced reduction of visual acuity on the low-contrast chart

Table II
Subjective changes

		1 hour	2 hours	3 hours	4 hours
atm	Fogging of vision	0	2 eyes	6 eyes	8 eyes
	Discomfort	0	0	6 eyes	6 eyes
atm	Fogging of vision	0	0	0	0
	Discomfort	0	0	0	0

e subjective changes were recorded continuously and in addition asked about specifically ach hourly examination

The examiner who did not need optical correction and did not wear contact ises experienced no subjective symptoms during the experiment

When the subjects were tested at normal atmospheric pressure but otherwise ider the same conditions as in the first experiment no subjective or objective anges of significance were noted

Discussion

ables II III and IV indicate all that sucjects wearing this type of contact lenses at altitude of 18 000 feet may not tolerate their lenses as well as they do at sea level obably the main cause for this is corneal epithelial hypoxia In this experiment no

Table III
Changes observed with the sl t lamp
he slit lamp examination was made without removing the lenses thus making staining chniques inapplicable For the same reason small degrees of sclerotic scatter were d fficult discern Corneal thickness changes differing less than 0 03 mm from the start point value were recorded as 0

		1 hour	2 hours	3 hours	4 hours
atm	Sclerotic scatter	0	0	0	0
	Ciliary injection	0	2 eyes	2 eyes	6 eyes
	Debris	0	6 eyes	10 eyes	10 eyes
	Corneal thickness	0	0	0	0
1 atm	Sclerotic scatter	0	0	0	0
	Ciliary injection	0	0	0	0
	Debris	0	0	0	0
	Corneal thickness	0	0	0	0

Table II
Changes in visual acu ty
The visual acuity was measured on a standard Monovers chart and also n a special low contrast chart us ng Snellen letters V s ial reduct on was onl reco ded whe amoi nted to one full l ne or more

		1 hour	2 hours	3 ho rs	4 hours
atm	Standard contrast	0	2 eyes	5 eyes	6 eyes
	Low c ntrast	0	2 eyes	4 eyes	4 eyes
1 atm	Stan lard contrast	0	0	0	0
	Lo v contrast	0	0	0	0

changes in corneal thickness v ere registered Corneal thickness changes suffic to cause significant change in the pachometry measurement would depend ma on stromal oedema O ir experiment was interrupted before there was time f stromal oedema to evolve The symptoms and signs developed by all sub indicate a corneal epithelial lesion but on sl t lamp examinat on no defe oedema of the epithel um could be ol served This may partly be due t the obscuring effect of the contact lenses The author bel eves that without lenses sclerotic scatter techniques and staining techn ques ld show ep thelial cha in keeping with the discomfort and visual reduct on experienced by the partic in this study This belief is supported by the increased amount of debris on the film which must originate from damaged epithelial ells

The contact lenses in common use today decrea e the oxygen ava lable t the cornea by a considerable extent This may cause pr t al problems for contact wearers travelling at high altitudes

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References

ırke Ch (19/6) Contact lenses at high altitude Experience on Everest south west Face 19"5 B it J Ophthal 60 479–480
tt I & Bieber M T (1968) The steady state d stribution of oxygen and carbon dioxide in he in vivo cornea Exp eve Res " 103–112
"lse K A & Mandell R B (1970) Effects of reduced oxygen tension at the corneal surface Ar h Ophthal (Chicago) 84 505 508
"ielser C K (1952) Relation of factors involved in maintenance of optical Properties of ornea to contact lens wear Arch Ophthal (Ch cag) 47 398–343
uacke C A   Augsburger A & Hill R M (1971) Epithelial s elling with oxygen "insufficiency Amer J Optom " 565–568

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THE SURFACE COAT ON HUMAN CORNEAL ENDOTHELIUM

BY

STEFFEN SPERLING[1] and STEEN ROJ JACOBSEN[2]

Scanning electron microscopy of human cadaver corneas revealed a selective binding of ruthenium red-osmium tetroxide to some substance coating the posterior endothelial surface. A coating material was not found on autolyzed cells, on denuded areas of the membrane of Descemet or on the anterior surface of endothelial cells. Partial digestion of the coating material by urokinase and trypsin suggests the presence of at least three different structural or chemical elements.

Key words cell coat – endothelium – human cornea – morphology – ruthenium red – scanning electron microscopy – trypsin – urokinase

A mixture of ruthenium red and osmium tetroxide precipitates some substance on the posterior surface of normal human corneas (Schröder & Sperling 1977; Jacobsen & Sperling 1978). A similar substance has been found between the trabecula in baboon, rabbit and human eyes (Segawa 1975; Harnish 1976; [illegible] et al. 1977).

Ruthenium red-osmium tetroxide reacts with a number of negatively charged large polymers and with some lipids (Luft 1964, 1966, 1971a, b). The complex polymer ruthenium red and osmium tetroxide is insoluble in ethanol and ethylenoxide. It can be studied by scanning and transmission electron microscopy

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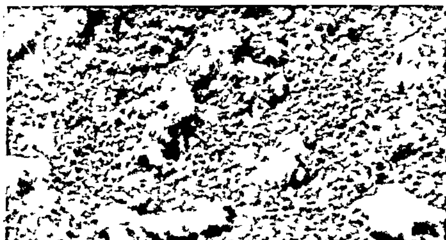


Fig 1
The posterior surface of corneal endothelial cells Fixed 14 h post mortem
Magnification 760 ×

Material and Methods

hole human eyes were enucleated from cadavers stored at 1 –?? C for 8–10 h and later at C Seven eyes were obtained 8–24 h post mortem and two eyes 64 and 71 h post mortem es were enucleated when no history of eye disease appeared from the case record and ien inspection revealed a normal cornea and a normal anterior chamber Corneas were cised with a 1 5 mm rim of sclera Three corneas obtained 64 71 and 18 h post mortem re fixed immediately after excision Three corneas were cut in thirds Each third was cubated in urokinase (Leo 2500 IU/ml) in trypsin (Novo 2 5 mg/ml) or in the basis edium without enzyme at 25 C for 15 30 or 60 min The enzymes were dissolved in a lanced salt solution (Ackroyd 19C4) In three corneas the endothelium was partially peeled f the membrane of Descemet with a fine forceps under a dissecting microscope

Corneas were fixed in equal parts of ruthenium red 15 p p m in distille l water 5% smium tetroxide and 0 ? N cacodylate buffer (pH 7 3) for 1½ h at ?5 C After fixation the ssue was transferred to cacodylate buffer dehydrated in graded ethanol critical point dried om carbon dioxide vacuum coate l with gold and examined in a Cambri lge Stereoscan)0 scanning electron microscope

Results

n the corneas fixed immediately after excision the posterior corneal surface of ntact cells was covered by a coherent layer The gross appearance of this layer is hown in Fig 1 The resolution power of the microscope does not allow definite onclusions regarding the structure of the coating material but high magnifications



Fig 2
Remnants of autolyzed end thel al cells on the membrane of Descemet.
Fixed 71 h post mortem Magnif at n 000 ×



F g 3
The end thelium was partially rem ved from the me b ne f Descemet Lef posteri r surface of endothel al cell in s tu Middle The a r surfa e f endothe on the everted edge of the coherent cell sheat Righ The mbrane of Descem t end th elium Fixed 12 h post mortem Mag n ×



Fig 4
• anterior surface of a coherent sheat of othelial cell after mechanical removal d 16 h post mortem Magnification 741×



Fig 5
Larger magnification of a detail in Fig 4 Magnification 3600 ×

e the impression that the layer was composed of spherical particles with meters of 100–200 nm aggregated without preferred orientation (Jacobsen & erling 1978)

On the two corneas obtained 64 and 71 h post mortem intact endothelial cells d partially autolysed cells were found In some areas the slightly ruffled surface the naked membrane of Descemet was visible In other areas cellular debris and mnants of intercellular borders were found No covering layer was found on ally or partially denuded areas of the membrane of Descemet or on autolysed ls (Fig 2) Nor was this material found on the anterior surface of the endo elium normally adhering to the membrane of Descemet (Figs 3 4 5)

On the anterior surface of the inverted cell sheat and on the membrane of scemet the intercellular borders were clearly outlined (Figs 3 4 5) In some eas protrusions of the intercellular borders with diameters 2–6 μm and finely anular surfaces appeared (Figs 4 5)

On the corneas treated by urokinase for 60 min three different structural mponents could be discerned in the surface material Spherical particles as those en on the untreated surface were in some places overlying whirled branching bers with diameters 200–250 nm (Fig 6) Adjacent to the cell surface branching raight fibers with diameters 100–150 nm were interwoven in a tight meshwork ig 7) In the corneas treated by trypsin for 30 and 60 min whirled fibers and attered remnants of coating material were found In the controls incubated in the lt solution for 60 min some of the spherical particles were missing and the hirled pattern could be discerned

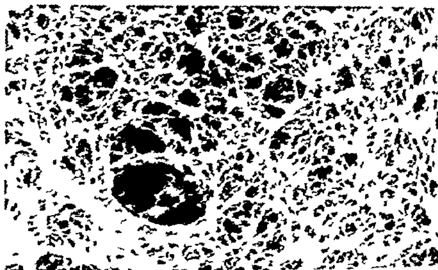


Fig 6
Whirled fibers Urokinase 15 min Magnification 1000 ×

Comments

A coating material was only found on the surface of intact endothelial cells in the anterior chamber The lack of this material in other locations rules out the possibility that it is an artefact produced by the ruthenium red-osmium technique alone Our present concept of the structure of the ruthenium red-osmium tetroxide fixed surface coat is illustrated in Fig 8



Fig 7
Stellate formations of straight fibers adjacent to the posterior cell surface Urokinase
Magnification 5000 ×

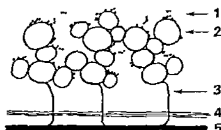


Fig 8

iatic drawing of our present concept of the structure of the coating material after n in ruthenium red-osmium tetroxide 1 Spherical particles aggregated without red orientation seen in Fig 1 2 Fibers in loose whirls seen in Fig 6 3 Centers of the configurations of straight fibers seen in Fig 7 4 Straight fibers 5 Outer limiting cell membrane (Pinx Pio Faborg)

elicate network of filaments between trabeculae in rabbit and baboon eyes was l in TEM pictures by Grierson et al (1977) when lower concentrations of nium red were used in the fixation Fibers were not observed by Scrøder & ing (1977) in TEM preparations of the coating material

egular polygonal outline of the cell borders facing the membrane of Descemet ound in the present study while a jig saw outline of cellular membranes was l close to the membrane of Descemet in rabbits by Hirsch et al (1977) when a fracture technique was applied A jig saw arrangement of the anterior cellular borders was also found in some human corneas after staining by ine red trypane blue (Sperling 1977) These observations suggest that methogical or individual differences rather than species differences account for epancies between the observed configurations of the basal cell borders in man abbits

is unlikely that the structure illustrated in Fig 8 represents the *in vivo* guration of the *coating material but this study indicates that at least three* rent structural or chemical components are present on the surface of intact thelial cells

Acknowledgments

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References

Ackroyd J F (1964) *Immunological methods* p 212 A symposium organized by the Co International Organization of Medical Sciences etc Blackwell Scientific P... Oxford

Grierson J Lee W R & Abraham S (1977) The appearance of the outflow appara... eye after staining with ruthenium red *Acta ophthal (Kbh) 55* 827–836

Harnish J P (1976) Elektronenmikroskopische Darstellung saurer Mukopolysacchar... Trabekelwerk *Klin Mbl Augenheilk 169* 90–94

Hirsch M Renard G Faure J P & Pouliquen Y (1977) Study of the ultrastructure of rabbit corneal endothelium by the freeze fracture technique Apical and lateral ju... *Exp Eye Res 25* 277–288

Jacobsen S R & Sperling S (1978) Scanning electron microscopic observations mucopolysaccharide coating om human corneal endothelium *Acta ophthal* (Kbh... 161–167

Luft J H (1964) Electron microscopy of cell extraneous coats as revealed by ruthen... staining *J Cell Biol 23* 54A–55A

Luft J H (1966) Fine structure of capillary and endocapillary layer as revealed by ruthe... red *Fed Proc 24* 1773–1783

Luft J H (1971a) Ruthenium red and violet I Chemistry methods of use for el... microscopy and mechanism of action *Anat Rec 171* 347–368

Luft J H (1971b) Ruthenium red and violet II Fine structural localization in anima... *Anat Rec 171* 369–416

Schrøder H D & Sperling S (1977) Polysaccharide coating of human corneal endothe... *Acta ophthal (Kbh) 55* 819–825

Segawa K (1975) Ultrastructural changes of the trabecular tissue in primary open a... glaucoma *Jap J Ophthal 19* 317–338

Sperling S (1977) Combined staining of corneal endothelium by alizarine red and tr... blue *Acta ophthal (Kbh) 55* 573–580

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NDOTHELIAL MORPHOLOGY RELATED TO DISEASE ACTIVITY IN HUMAN CORNEAS

BY

THOMAS OLSEN and STEFFEN SPERLING

Twenty normal and four groups of pathological corneas with the diagnoses aphakia macula after herpetic keratitis Fuchs endothelial dystrophy and graft rejection were sta ned with trypane blue and al zarin red The morphology of the endothelium was described in terms of cell dens ty coeff cent of variation for cell area percentage of hexagonal cells percentage of jo nt meetings of more than three cells nuclei per cell and nuclear shape
The groups of aphak a kerat tis Fuchs dystrophy and graft rejection were cons dered to represent increas ng degrees of endothel al disease acti ity at the t me of evaluation The only parameter show ng cons stent variation w th d sease acti ity was the percentage of jo nt meetings of more than three cells

Key word al zarin red – endothel um cornea morphology trypane blue

normal human corneas a coherent monolayer of endothelial cells covers the sterior surface of the membrane of Descemet Each cell is surrounded by four to ht cells The borders between neighbouring cells meet at angles approximating) Pointed angles and joint meetings of more than three cells are rare Each cell nta ns one globular or slightly ovo d nucleus (Sperling 1978a)

When a single endothelial cell is damaged it is sloughed off the membrane of scemet by neighbouring cells who in turn spread and cover the defect The ghbouring cells radiate towards the center of the dead cell and form a joint eting Later the cells slide and reform a normal pattern During reformation of : cellular pattern the cells occur in constellations characterized by converging

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pointed angles and joint meetings of four and five cells (Oh & Evans 1960 Sp... 1976 Olson et al 1978 Sperling 1978 Olsen 1979)

After endothelial trauma or disease the numerical cell density decreases ... cells become binucleate and multinucleate Large variations in cellular and ... size and shape appear (Nagano 1914 Stocker 1953 1971 Binder & B... Chi et al 1960 1962 Shierhölter & Honegger 1975) The percentage of hex... cells has been shown to decrease after cataract extraction and with decrea... density in normal eyes (Olsen 1979a)

This study was undertaken in order to investigate whether deviations fr... normal endothelial pattern could be related to disease activity For the purp... this study four groups of corneas were selected These groups were reg... representing different disease activities at the time of evaluation

Material and Methods

Twenty normal and five aphakic eyes were enucleated from cadavers stored at 15 ... 6–10 h later at 10°C Eyes were regarded normal when no history of eye disea... indicated in the case record and when the cornea and the anterior chamber appeared ... by simple inspection. Mean patient age 56 7 years range ?–83 The aphakic eyes had b... subjected to operation 4–9 years previously Patient age ranged 61–85 years. Whole e... were excised with a scleral rim. Endothelial cell borders and nuclei were stained with ... red and trypane blue (Sperling 1977) Six mm central buttons were cut from the end... side after staining Eleven corneal buttons were obtained from patients undergoing pe... ing keratoplasty The diagnoses were Macula after herpetic keratitis (5) Fuchs endo... dystrophy (3) and graft rejection (3) Patient age range in the three groups were ... 57–74 and 36–71 years respectively The buttons were stained by alizarin red and try... blue immediately after removal

Buttons were bisected before wet mount on microscope slides with the endothelium fa... the cover glass Photomicrographs were obtained on Kodak Tri-X film (24 × 36 mm magnification 40 × 8 5 secondary enlargement to 12 ? × 1? 8 cm On central buttons ... normal corneas the microscope was successively centered in predetermined points ... cribed by Sperling (1978a) and six or more photographs were obtained of areas ... least three quarters of a full field could be brought into focus From pathological b... four or more photographs were obtained from flat areas with cell cover

For evaluation of cell morphology four photographs from each cornea were selected ... the basis of the largest photographic clarity by a technician unaware of the purpose of ... study On each photograph a frame of ?2 × 10? mm corresponding to a corneal area of ... mm² was drawn in the area of the largest photographic clarity

The following morphological characteristics were recorded 1) Endothelial cell dens... estimated according to Sperling & Gundersen (1978) 2) Cell size Cells from all pa... corneas and from twelve normal corneas chosen at random were grouped according to ... point counting as described by Elias et al (1971) A point distance of 6 19 mm correspond... to 8 ? µm on cornea was chosen because this turned out to be the minimum measure of ... size 3) Number of neighbours per cell 4) Number of cells in point meetings 5) Numbe... nuclei per cell 6) The ratio between the largest and the smallest nuclear diameter

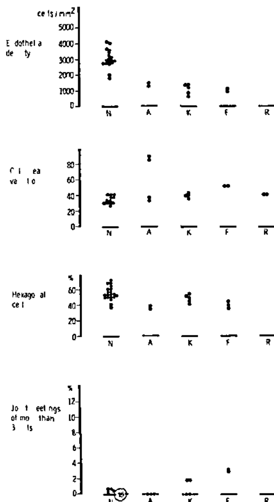


Fig 1

rphological characteristics of normal and pathological endothelial cells N = normal A = akia K = macula after herpetic keratitis F Fuchs dystrophy R = graft rejection Cell area variation = $\frac{S \quad 100}{\bar{x}}$ %

Results

either pathological group the mean cell density was lower than in the normal oup In one normal cornea from a male patient of 50 years a cell density of 5634 ls/mm² was found This finding is so unusual that this cornea was excluded from imates of normal values Mean numbers of cells pr mm² (±SD) were Normal = 19) 3101 ± 732 aphakic 1254 ± 363 keratitis 1080 ± 303 Fuchs 1334 ±

602 rejection 891 ± 716 cells/mm² (Groups N A K F and R in Fig 1) is not correlated to cell density in the normal group ($r = -0.31$ $2P$ = ... $n = 19$)

In 12 normal and in either pathological group the cell area variation incr... with increasing mean cell size When the relative cell area variation (coeffic... variation $\frac{SD}{\bar{x}}$ was related to mean cell size this was not the case For normal cor... $r = 0.21$ ($2P = 0.32$ $n = 12$) Coefficients of variation within the normal range w... found in the keratitis group (K) Normal and high values were found in the aph... group (A) whereas slightly elevated values were found in Fuchs dystrophy (F) ... in the rejected grafts (R)

The number of neighbours per cell was counted Mean percentages of hexa... cells were 58 ± 9 ($n = 19$) 43 ± 16 48 ± 5 39 ± 5 and 30 ± 9 per cent in grou... A K F and R respectively (Fig 1) For either group a direct relationship was fo... between endothelial cell density and the percentage of hexagonal cells (Fig 3 ... normal corneas $r = 0.53$ ($2P < 0.05$ $n = 19$)

The number of cells in joint meetings was counted Joint meetings of four c... were found in five out of twenty normal corneas in one out of five in the aphaki... group in three out of five in the keratitis group and in all corneas in the dystr... and rejection groups In one cornea from the dystrophy group and in one fro... rejection group joint meetings of five cells were found No joint meetings of ...

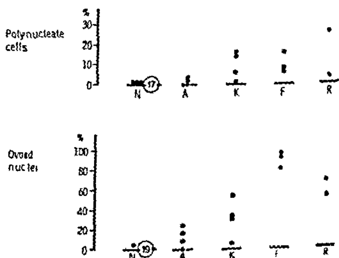
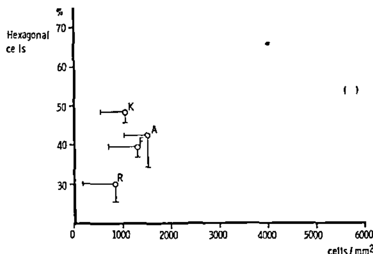


Fig 2

Nuclear characteristics of normal and pathological endothelial cells N = normal A = aphakia K = macula after herpetic keratitis F = Fuchs endothelial dystrophy R = graft rejection Ovoid nuclei signify nuclei in which the ratio between the largest and the smallest diameter was > 1.5 1



F g 3

rcentage of hexagonal cells related to cell dens ty Normal corneas are nd cated bv closed cles For pathological corneas mean values are nd cated bv open circles Standard iat ons are ind cated by bars A = aphak a K macula after herpet c keratit s F Fuchs dothel al dystrophy R graft reject on For normal corneas r 0 53 ($2P < 0\ 05$ n 19)

an five cells were found Borders between cells in jo nt meetings of four cells met angles approximating 90 and these cells were surrounded bv cells without nverging po nted angles

Nuclei per cell were counted and the nuclear shapes were recorded Multinu ated cells and cells with nuclear diameter ratios > 1 5 I were rare in the normal rneas but frequent in either pathological group (Fig 2)

Comments

thological corneas with d ffering disease activity were chosen for the present idy Aphakic eyes had been subjected to operation 4 9 years previously No d cation of corneal disease was found at the t me of evaluat on In the corneas ith macula after herpetic keratitis signs of acute inflammation had been absent r months Fuchs dystrophy was chosen as an example of low grade current idothelial damage at the t me of evaluation and graft rejection as an example of gh grade current damage to the endothel um (Olsen 1979)

In order to ind cate d sease activity a morphological characterist c should vary adually through the groups Aphakia keratitis dystrophy and rejection This was

not the case for cell density cell area variation percentage of hexagonal cells per cell or nuclear shape The percentages of joint meetings of more than three cells increased with increasing disease activity The highest values occurred in the group of rejected grafts and the lowest in corneas from normal and aphakic eyes This suggests that the frequency of joint meetings of more than three cells could be regarded as an indicator of disease activity

After injury of a single endothelial cell neighbouring cells radiate towards the centre of the damaged cell The constellation of 5–8 neighbouring cells in a joint meeting (Figs 4b 4c) have been termed *a rosette* (Oh & Evans 1961) During reformation of rosettes the cells slide and occur in the constellations shown in Fig 4d–h These constellations have been termed *reformation figures* (Sperling 19… The patterns Fig 4d–h are characterized by cells with converging pointed a… and joint meetings of more than three cells

The cells in joint meetings of four found in the present study did not appear … reformation figure constellations Borders between cells met at angles approximating 90 and they were surrounded by cells without converging pointed a…

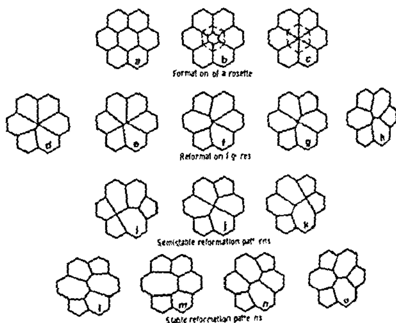


Fig 4

a–c Formation of a *rosette* a joint meeting of six originally hexagonal cells d–h *Reformation figures* formed by retraction of one two or three cells (dotted) from the rosette i… Semistable reformation patterns characterized by joint meetings of four cells and … angles l–o Stable cell patterns characterized by joint meetings of three cells and … angles

.ıis observation suggests that rosettes are not necessarily reformed to joint :eetings of three cells within hours as reported by Sherrard (1976) and Sperling 978) Intermediate semistable constellations of four cells without pointed angles in principle in Fig 4 i–k may stay for extended periods of time before formation to stable cellular patterns (Fig 4 l–o) In the present study it was und that the frequency of semistable cell constellations was correlated to disease tivity

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References

ınder R. F & Binder H F (1957) Regenerative processes in the endothelium of the cornea *Arch Ophthal. (Chicago) 57* 11–13

ıı H H Teng C C & Katzin H M (1960) Healing process in the mechanical denudation of the corneal endothelium *Amer J Ophthal 49* 693–703

ıı H H Teng C C & Katzin H M (1962) Histopathology of corneal endothelium *Amer J Ophthal 53* 215–235

ıas H Hennig A & Schwartz D E (1971) Stereology Applications to Biomedical Research *Physiol Rev 51* 158 200

ıgano (1914) Untersuchungen zur Pathologie des Hornhautsendothels *Arch Augenheilk* 76 96–68

h J O & Evans C S (1960) Suppressive effects of pyrilamine maleate and d lysergic acid diethylamide (LSD 25) on early corneal lesions produced in vitro by Newcastle Disease Virus (NDV) and compound 48/80 *Virology 10* 127–143

lsen T (1979) The specular microscopic appearance of corneal graft endothelium during an acute rejection episode *Acta ophthal (Kbh) 57* 882–890

lsen T (1979a) Variations in endothelial morphology of normal corneas and after cataract extraction A specular microscopic study *Acta ophthal. (Kbh) 57* 1014–1019

lson L E Marshal J Rice N S C & Andrews R. (1978) Effects of ultrasound on the corneal endothelium II the endothelial repair process *Brit J Ophthal 62* 145–154

hierholter R & Honegger H (1975) Morphology of the corneal endothelium under normal conditions and during regeneration after mechanical injury *Adv Ophthal 31* 34–99

ıerrard E S (1976) The corneal endothelium in vivo Its response to mild trauma *Exp Eye Res 22* 347–357

›erling S (1977) Combined staining of corneal endothelium by alizarin red and trypane blue *Acta ophthal (Kbh) 55* 1 8

›erling S (1978) Early morphological changes in organ cultured human corneal endothelium *Acta ophthal (Kbh) 56* 785–792

›erling S (1978a) Indirect evaluation of numerical density of corneal endothelial cells *Acta ophthal (Kbh) 56* 445–454

Sperling S & Gundersen H J G (1978) The precision of unbiased estimates of
density of endothelial cells in donor corneas *Acta ophthal (Kbh)* 56 793–80
Stocker F W (1953) The endothelium of the cornea and its clinical implications *Tr*
ophthal Soc 51 669–786
Stocker F W (1971) *The endothelium of the cornea and its clinical implications* 2nd ed. T
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ON THE SIGNIFICANCE OF A LOW ENDOTHELIAL CELL DENSITY IN FUCHS ENDOTHELIAL DYSTROPHY A SPECULAR MICROSCOPIC STUDY

BY

THOMAS OLSEN

In order to verify whether a low endothelial cell density is a primary event in Fuchs endothelial dystrophy a specular microscopic examination was attempted in 20 patients with Fuchs dystrophy Most of these patients had previously undergone cataract extraction In five patients only was it possible in places to observe endothelial cellular outline to such an extent that the cell density could be estimated The resulting estimates ranged from ˜15 to 2380 cells mm² and were not as a group found to be lower than in a control group of aphakic subjects This finding is evidence against the view that Fuchs endothelial dystrophy is a low cell density syndrome

Key words cornea – endothel um – Fuchs endothelial d strophy – pecular microscopy

hs endothelial dystrophy is a clinical diagnosis usually applied to the combina of corneal oedema and characteristic abnormalities in the posterior limiting rs of cornea as seen with the biomicroscope and called "guttae" after Vogt 10) In the past numerous attempts have been made to describe the pathological tomical features of this disease the site of which is generally considered to be the othelium (Irvine 1956 Chi et al 1958 Stocker 1971 Iwamoto & de Voe 1971 ella 1971 Hogan 1974) The finding of a low endothelial cell density has led is investigators to consider the compromised barrier function of the endo- ium to be due to a low and inadequate number of cells Such a hypothesis would

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fit nicely with the association of Fuchs' disease with age and cataract extraction [illegible] of which factors are known *to decrease the endothelial cell density*.

Most studies on the endothelium in Fuchs' dystrophy have largely been [illegible] specimens removed at keratoplasty. That is at the end stage *of the disease* [illegible] therefore be questioned whether *the low cell density* is a primary or a [illegible] *finding in this* disease. With the introduction of the specular microscope [illegible] *1968*; Laing et al. 1975; Bourne & Kaufman 1976; Sturrock & Sherrard [illegible] Olsen 1979) it is *possible to* examine, photograph and quantitate the [illegible] *morphology of the endothelium in vivo. Therefore it is now theoretically* [illegible] detect the earliest changes in the endothelium associated with Fuchs' disease.

The purpose of the *present study* was to present data on endothelial [illegible] *morphology* in early stages of Fuchs' endothelial dystrophy as it is seen [illegible] specular microscope. The aim of the study has especially been concerned [illegible] endothelial cell density in this disease.



Fig. 1

The endothelial reflex in two patients with Fuchs' endothelial dystrophy. Top: [illegible] years of age, cataract extraction 2 years previously with 1 year history of [illegible] Central corneal thickness 0.60 mm. Estimated cell density [illegible] cells/mm².
Bottom: woman, 78 years of age, cataract extracted 15 years previously with [illegible] of corneal oedema. *Central corneal thickness 0.66 mm*. Estimated cell den[illegible]
Arrows point to the smallest defects in the reflex which showed a tendency to be [illegible] to cell joints. Bar indicates 100 μm.

Subjects and Methods

tal of 20 patients with Fuchs endothelial dystrophy were examined with the non-contact ular microscope (Olsen 1979) They all fulfilled the following criteria (Waring et al) 1) corneal oedema with bullae and 2) guttae present in the endothelium as seen with slit lamp

the great majority of these patients endothelial cellular details were not detectable either to extensive opacification of the cornea or absent reflex from the endothelium In the ainder (5 patients) it was possible in places to obtain a number of photographs of discrete s with visible cells One of these patients a 56-year-old male had no other history of eye ase whereas the remaining four patients (age range 67-81 years) had had cataract surgery ormed one one and a half six and thirteen years prior to onset of the disease In ospect there was evidence of dystrophic changes present in the endothelium in all patients r to the cataract surgery The duration of symptoms prior to specular microscopic mination was between one half to four years

hotographs were taken as centrally as possible (always more than about 3 mm from the ous) along a horizontal line through the center of the cornea This was done to ensure a tant distance from surgical wounds at the upper limbus Counting of the cells was done as ribed earlier (Olsen 1979) by drawing a number of frames on the photomicrographs and wing an unbiased counting technique Due to the discrete areas in which endothelial cells ld be seen smaller frames had to be used however The total area of endothelium thus nted varied from 0 031 to the normally used area of 0 054 mm²

he use of the smaller sample area would tend to increase the standard error of the mate by approximately the square root of the ratio between the smaller and the normal nple area i e about thirty percent Assuming a normal standard error of 4 % (Olsen 9) this would increase to 5 2 % using the smallest sample area i e still a rather low figure

s a control group eight aphakic patients who successively came to cataract surgery on the er side were photographed and had their central endothelial cell densities estimated ne of these patients showed cornea guttata or had abnormal corneal thickness Mean age 63 years range 36-78 Time range after operation was between one half to three years

Results

e typical specular microscopic appearance of the endothelium in Fuchs dys phy was that of numerous confluent reflex free areas (Fig 1) In the majority of examined patients these changes were so extensive that they concealed cellular tails completely In five patients it was posible to detect cellular details in areas of e endothelium large enough for estimates of the cell density to be drawn These eas were detected by carefully scanning the endothelium and photographs were ostly obtained at the periphery of the more centrally located oedema At such ints the reflex free areas could be brought to vary in size by slightly adjusting the using depth or the angle of incident slit illumination illustrating that they really re excrescences on Descemet s membrane and not cell free or pigmented areas characteristic feature of the smallest reflex free areas was the tendency to be ated close to points where more than two cells met (arrows in Fig 1)

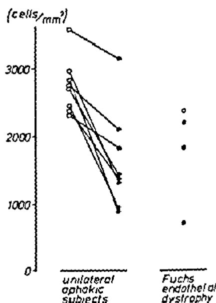


Fig 2

Estimated endothelial cell density in five patients with Fuchs endothelial dystr... group of cataract extracted patients Closed circles signify cataract extracted eyes ... circles are from the same patient

Estimated endothelial cell densities ranged from 715 to 2380 cells ... appear in Fig 2 together with estimates from the unilateral aphakic pat... seen that only in one instance did the cell counts from the group ... endothelial dystrophy fall below that of the aphakic group The cell dens... one patient without previous cataract extraction fell within the normal ... unoperated fellow eyes

Discussion

The present study has shown that a decreased endothelial cell densit... obligatory finding in Fuchs endothelial dystrophy This indicates the barrier function of the endothelium not to be simply a low cell density sym...

The five patients reported on in this paper were selected on the basis of ... to observe the endothelium so that only patients without marked cornea... and without completely deranged endothelium had their endothelial cel... estimated These patients must be considered to represent earlier sta... disease as compared to patients in which cellular details could not be obser...

It may be objected that the specular microscope only reveals areas with...

rescences on Descemet s membrane so that the estimates of endothelial cell sity are not representative of the whole endothelium Flattening of cells over n excrescences have also been described (Vogt 1930 Irvine 1956 Chi et al 8 Kloucek 1967 Iwamoto & De Voe 1971 Hogan et al 1974) Therefore oretically the increased permeability could still be explained as a low cell density alized at such points In normal endothelia if cells are damaged neighbouring s spread to cover the defect. Even after such immediate healing response the lothelial cells have a capability of moving towards regions of lower cell density as been shown after cataract surgery (Rao et al 1978) Therefore if a decrease in lothelial cell density was the primary event in Fuchs endothelial dystrophy a tain smoothing out of differences in cell density would have occurred The bility to demonstrate a low endothelial cell density in the present study therefore icates that the disease is not initiated by a low number of cells *per se* The cell nsities reported in the present study are far above the lowest cell densities ountered in corneal grafts with normal hydration (Bourne & Kaufman 1976a)

What really causes the disease remains unclear Defects in the fibrinolytic system e been described (Bramsen & Stenbjerg 1979) but how the increase in rinolytic activity acts on the cornea is unknown Evidence that the abnormal dothelial permeability is of intercellular origin may be found in the observed idency for small reflex free areas to be located close to cell meetings (Fig 1) ese small areas may be interpreted as localized subendothelial oedema pushing cell membranes posteriorly whereby the light is reflected in other directions Evidence that an active cell death is present has also been reported (Olsen & erling 1980) The low cell density seen in the end stage of the disease may therefore rather be the result and not the cause of the disease

Acknowledgments

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References

urne W M & Kaufman H E (1976) Specular microscopy of human corneal endothelium n vivo *Amer J Ophthal 81* 319–323

urne W M & Kaufman H F (1976a) The endothelium of clear corneal transplants *Arch Ophthal (Chic go) 94* 1730–1739

amsen T & Stenbjerg S (1979) Fibrinolytic factors in aqueous humour and serum from patients with Fuchs dystrophy and patients with cataract *Acta ophthal. (Kbh) 57* 470 475

pella J A (1971) The pathology of corneal endothelium *Ann Ophthal 3* 397–400

Chi H N Teng C C & Katzin H M (1958) Histopathology of primary endothelial epithelial dystrophy of the cornea *Amer J Ophthal 45* 518–535
Rao G N Shaw E L Arthur E & Aquavella J V (1978) Morphological appearance of healing corneal endothelium *Arch Ophthal (Chicago) 96* 2027–2030
Hogan M J Wood I & Fine M (1974) Fuchs endothelial dystrophy of the cornea *Amer J Ophthal 78* 363–383
Irvine A R (1956) The role of the endothelium in bullous keratopathy *Arch Ophthal (Chicago) 56* 338–351
Iwamoto T & De Voe A G (1971) Electron microscopic studies on Fuchs combined dystrophy Posterior portion of the cornea *Invest Ophthal 10* 9–28
Kloucek F (1967) The corneal endothelium *Acta Univ Carol Med 13* 321–343
Laing R A Sandstrom M M Leibowitz H M (1975) In vivo photomicrographs of the corneal endothelium *Arch Ophthal (Chicago) 93* 143–145
Maurice D M (1968) Cellular membrane activity in the corneal endothelium of the intact eye *Experientia 24* 1094–1095
Olsen T (1979) Non-contact specular microscopy of human corneal endothelium *Acta ophthal (Kbh) 57* 986–998
Olsen T & Sperling S (1980) Endothelial morphology related to disease activity in human corneas *Acta ophthal (Kbh) 58* 103–110
Rao N G Shaw E L Arthur E & Aquavella J V (1978) Morphological appearance of healing corneal endothelium *Arch Ophthal (Chicago) 96* 2027–2030
Stocker F W (1971) *The endothelium of the cornea and its clinical implications* ed 2 Charles C Thomas Springfield Ill
Sturrock G D Sherrard E S & Rice N S C (1978) Specular microscopy of the corneal endothelium *Brit J Ophthal 62* 809–814
Vogt A (1930) *Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges* Julius Springer Berlin
Waring G O Rodrigues M M & Laibson P R (1978) *Corneal dystrophies II Endothelial dystrophies* Surv Ophthal 23 147–168

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TRIFLUORTHYMIDINE IN THE TREATMENT OF HERPES SIMPLEX CORNEAL ULCERS

A clinical evaluation

BY

PREBEN GILBERT and KRESTEN WORK

The treatment of herpetic corneal ulcerations with trifluorthymidine (F3T) has been evaluated in a clinical trial F3T was found to be an effecti e anti iral agent for herpetic keratitis and a valuable alternati e to idoxuridine (IDU) therapy Clinically IDU – resistent herpetic ulcers responded favourably to treatment with F3T

Key words herpes simplex virus – keratitis – trifluorthymidine – idoxuridine

ʼatment of herpetic corneal ulcers with idoxuridine (IDU) is unsatisfactory as a ›portion fail to heal and some patients develop signs of toxicity or hypersensitivity IDU Unfortunately these are often the individuals most in need of antiviral rapy for herpes simplex keratitis Trifluorthymidine (F3T) has proved a nificantly superior alternative to idoxuridine (Wellings et al 1972) being iformly effective in cases failing to heal with IDU therapy and in cases with a ›ersensitivity reaction to IDU (McGill et al. 1974)

3T has a structure similar to that of IDU differing only in a side group It is ısiderably less toxic to the cornea (Kaufmann & Heidelberger 1964 Holtmann & ın 1977) and is also ten times more soluble In tissue culture F3T inhibits viral ›lication at the lowest concentration of any analogue yet tested (Umeda & ıdelberger 1969) In solution F3T is rather unstable at neutral pH and storage 4 5 days at 5 reduces the concentration by approximately 50%

The present investigation is a clinical evaluation of the effectivity of F3T in the ʼatment of herpes simplex corneal ulcers

ei ed July 5th 1979

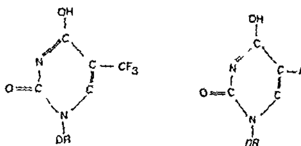


Fig 1
Structural formulae of trifluorthymidine and idoxuridine (DR = desoxyr...

Material and Methods

Consecutive typical cases of dendritic or amoeboid ulcerations of the ... referred to the department over a 8 month period were included in the ... Twenty four patients had dendritic keratitis and five patients had ... ulcerations Nine patients received IDU treatment over a period of ... immediately before being taken into the F3T trial

Treatment was carried out on an outpatient basis with 1% F3T Crystal... was dissolved in physiologic saline without preservative and sterilized by ... It was emphasized to the patient that one drop had to be instilled 6 times da... that the bottle should be kept in the refrigerator Due to the instability of available F3T solution a fresh bottle was dispensed every four days through... period of treatment

History and examination were recorded The ulceration was drawn ... photographed and the initial size estimated Follow up examinations were ... med as near to daily as possible for the first four days and thereafter on ... days The treatment was continued for a minimum period of eight days ... was considered to have been completed when there was no visible ulcera... staining with either fluorescein or Bengal rose using the slitlamp

Results

All dendritic ulcers healed within two weeks from the beginning of trea... F3T

Ten small dendritic ulcers (< 5 mm) healed in 2 8 days with an average ... days

Fourteen large dendritic ulcers (≥ 5 mm) healed in 3 14 days with an ave... 5 9 days

he five amoeboid ulcerations healed in 7—18 days Nine patients had what was sidered to be IDU resistent ulcers and all healed with F_3T after having been ted unsuccesfully with IDU for 1 3 weeks

Discussion

the present study we found F_3T to be a valuable alternative to IDU in the itment of herpetic keratitis Most lesions healed within one week and we did not any failures

one of our patients with superficial epithelial lesions were seen to develop mal keratitis This might be due to the greater solubility of F_3T as compared h IDU allowing F_3T to penetrate sufficiently into the cornea to inhibit virus lication deep in the stroma

n this series we did not note any signs or symptoms that could be ascribed to icity of F_3T Nor did any of our patients develop any signs of allergy to the drug is is very encouraging when dealing with a drug that seems to be considerably re active than IDU F_3T occasionally produces a contact dermatitis similar to that iduced by IDU and in some cases signs of corneal epithelial toxicity will develop h the earliest sign being punctate erosions If the treatment is continued frank thelial oedema without stromal swelling is produced These signs quickly subside er F_3T has been stopped (McGill et al 1976) The absence of allergic and toxic e effects in the present investigation is in accordance with other clinical and perimental studies Thus Wellings et al (1972) observed no side effects in 40 ients treated with F_3T for a 2 week period In eight patients with contact rmatitis due to IDU hypersensitivity F_3T was substituded and in no instance did hypersensitivity reaction occur (MaGill et al 1974) In controlled animal experi nts (Kaufmann & Heidelberger 1964) F_3T did not produce toxic effects in the bit cornea when administered 2 hourly round the clock for two months ltmann & Stein (1977) found no delaying effect of F_3T on epithelial regenera n in the rabbit cornea

Finally we noticed that generally the discomfort of the patients due to the rpetic affection disappeared after a few days of treatment and long before aling of the cornea was completed Quite often the affected eyes were pale and e patients free of symptoms after one or two days of F_3T treatment enabling em to resume their usual activities

In conclusion we feel that F_3T offers a valuable alternative to IDU therapy for rpetic ulcers

References

Wellings P C Awdry P N Bors F H & Jones B R. (1977) Clinical eva… trifluorthymidine in the treatment of herpes simplex corneal ulcers Amer J C… 932–942

McGill J Holt Wilson A D McKinnon J R Williams H P & Jones B R (1974) … aspects of the clinical use of trifluorthymidine in the treatment of herpetic ulcer… cornea Trans ophthal Soc U K 94 342–352

Kaufmann H E & Heidelberger C (1964) Therapeutic antiviral action of 5-trifluor… 2-deoxyuridine in herpes simplex keratitis Science 145 585–590

Holtmann H W & Stein H J (1977) Zur Frage der Epithelregenerationsfähigkeit… Trifluorthymidine Behandlung (F3TDR) Klin Mbl Augenheilk 171 576–579

Reyes P & Heidelberger C (1965) Fluorinated pyrimidines XXVI Mammalian thymidylate… syntetase its mechanism of action and inhibition by fluorinated nucleotides… Pharmacol I 14–30

Umeda M & Heidelberger C (1969) Fluorinated pyrimidines XXXI Mechanism… inhibition of vaccinia virus replication in HeLa cells by pyrimidine nucleosides Proc… exp Biol N Y 130 24–29

Sundmacher R (1978) Trifluorthymidineprophylaxe bei der Steroidtherapie herpetischer… Keratouveitiden Klin Mbl Augenheilk 173 516–519

McGill J Fraunfelder F T & Jones B R (1976) Current and proposed management… Ocular herpes simplex Surv Ophthal 20 358-365

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CLINICAL TRIAL OF THE TOPICAL USE OF DISODIUM CROMOGLYCATE IN VERNAL ALLERGIC AND CHRONIC CONJUNCTIVITIS

BY

MARKKU LEINO and ERKKI TUOVINEN

Thirty three patients were treated with disodium cromoglycate (DSCG) Of these 5 had vernal conjunctivitis 18 had allergic conjunctivitis and 10 had mild chronic conjunctivitis in which the exact aetiology could not be determined 70 % of patients with DSCG as the only medication achieved at least some beneficial effect being almost exlusively in the groups of either vernal or allergic conjunctivitis The basic trend seemed to indicate a reduction in severity during the treatment with DSCG in allergic diseases

Key words vernal keratoconjunctivitis – allergic conjunctivitis – chronic conjunctivitis – disodium cromoglycate

he therapeutic efficacy of disodium cromoglycate (DSCG) in bronchial asthma is nerally accepted The administration of DSCG has reduced the requirement for roid therapy in many patients with chronic asthma It is often very useful in cercise induced asthma but it can be helpful in all types of asthma

DSCG inhibits the release of chemical mediators in immediate IgE mediated persensitivity *particularly those involving mast cells DSCG is thought to stabilize* some way the outer layers of mast cells (Mansell et al) It is suggested that DSCG terferes with Ca transport across the mast cell membrane (Foreman et al)

The study presents the results of a clinical trial with DSCG in patients with vernal lergic or mild chronic conjunctivitis

eived May 29 1979

Material and Methods

Thirty three outpatients referred to the Department of Ophthalmology University Hospital of Kuopio during May 1977 to July 1978 were treated Lomudal® eye drops which were not yet registered for general use in Finland time of the trial

The diagnoses of allergic conjunctivitis were based on a positive history conjunctival scrapings for eosinophilic leucocytes In the allergic group patients had negative scrapings for eosinophilic leucocytes but the symptoms history suggested an allergic etiology In addition bacterial and chlamydia were performed Two patients who had positive chlamydia cultures (with scrapings for eosinophilic leucocytes) were excluded from the trial One patient the allergic group had a scanty conjunctival growth of Staphylococcus Besides the latter patient none of the patients in the trial had either bacterial or chlamydia cultures

The five patients with vernal conjunctivitis had all previously received topical steroid therapy Similarly most of the 18 patients with allergic conjunctivitis and the 10 patients with mild chronic conjunctivitis had previously symptomatic and anti allergic topical and systemic medication Observation varied from less than a week to 30 weeks averaging a good seven weeks patients with an allergic conjunctivitis had a short observation time because prompt favourable response and due relief of symptoms with the recession allergic season In one case of chronic conjunctivitis an apparently harmless effect led to the discontinuance of treatment only a few days after commencement

The drops were instilled usually four times daily in both eyes although conjunctivitis often 5 6 times a day The patients were inquired for the symptoms itching soreness grittiness discharge photophobia and possible symptoms Six patients also received topical steroids and or other medication (Table I)

Results

The patients with either vernal or allergic conjunctivitis responded favourably the treatment most of whom became either symptomless or nearly during treatment Two patients with mild allergic conjunctivitis apparent relief of symptoms In the chronic conjunctivitis group the response generally insignificant

At the end of observation time the treatment was discontinued for chronic conjunctivitis patients because of insufficient clinical response (Table

Table I
Control of eye disease with Lomudal[8]

	Fully controlled	Partly controlled	Useful response	Poor response	No response
nal conj					
DSCG alone	2	0	0	0	0
DSCG + other therapy	1	2	0	0	0
ergic conj					
DSCG alone	9	2	3	1	1
DSCG + other therapy	1	1	0	0	0
r nic conj					
DSCG alone	1	2	0	3	3
DSCG + other therapy	1	0	0	0	0

lly controlled = complete or nearly complete relief of symptoms Partly controlled = a stinct relief of symptoms but patient not completely satisfied Useful response = some relief symptoms but patient *not nearly satisfied Poor or no response = no distinct relief of* mptoms

Table II
Severity of eye disease before treatment and at the end of observation time

Severity	Vernal conj		Allergic conj		Chronic conj		Total	
	Before	After	Before	After	Before	After	Before	After
Absent	0	2	0	11	0	3	0	16
Mild	0	3	7	[illegible]	5	6	12	16
Moderate	3	0	[illegible]	0	5	1	15	1
Moderate/Severe	1	0	2	0	0	0	3	0
Severe	1	0	2	0	0	0	3	0
Total	5	5	18	18	10	10	33	33

bsent = no symptoms Mild = discomfort and inconvenience just noticeable Moderate = iscomfort and inconvenience most of the day but does not interfere with daily routine Moderate to severe = discomfort and inconvenience noticeable most of the day and interference with normal daily activity (e g work reading watching TV dri ing) Severe = otal daily routine disrupted

continued for over half (10 out of 18) of the allergic conjunctivitis pat
continued for all of the vernal conjunctivitis patients

In many cases the allergic season was over at the end of observation time a
treatment was no longer required in the allergic conjunctivitis group of pa

A useful response was observed in 21 patients in the allergic and
conjunctivitis group but only in four patients in the chronic conjunctivitis g
statistically significant ($P < 0.005$) difference exists between these two
(contingency method)

Table II conveys a general trend towards improvement in the vernal and
conjunctivitis patient groups The side effects which were encountered
patients were mild foreign body or burning sensations on application of
led to discontinuance of the medication in the other patient

The results of this study conform with results obtained in other trials wi
(Easty et al Greenbaum et al Kazdan et al Tabbara et al) The scar
vernal disease was a surprise possibly related to the Northernly location of
where the trial was carried out

References

Easty D L Rice N S C & Jones B R (1972) Clinical trial of topical disodium crom in vernal keratoconjunctivitis *Clin Allergy* 2 99–107

Foreman J C & Garland L G (1976) Cromoglycate and other antiallergic drugs a mechanism of action *Brit Med J* 1 820–1

Greenbaun J Cockcroft D Hargreave F E & Dolovich J (1977) Sodium cromogl ragweed allergic conjunctivitis *J Allergy* 59 437–9

Kazdan J J Grawford J S Langer H & MacDonald M I (1976) Sodium cromogl the treatment of vernal keratoconjunctivitis and allergic conjunctivitis *Ca J Oph* 300

Mansell A Dubrowsky C Levison H Bryan A C Langer H Collins-Williams C R I (1974) Lung mechanisms in antigen induced asthma *J appl Phys* ...

Tabbara K F & Noureddine T A (1977) Cromolyn effects on vernal keratoconj children *Arch Ophthal (Chicago)* 95 2184–2186

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TRAUMATIC HYPHAEMA TREATED AMBULATORY AND WITHOUT ANTIFIBRINOLYTIC DRUGS

BY

A K. SJØLIE and K. KAMP MORTENSEN

Forty four patients referred consecutively over a period of one year for treatment of traumatic hyphaema have been treated ambulatory and with no drugs
Four patients developed secondary haemorrhage three regained normal visual acuity
The frequency of secondary haemorrhage is not statistically different from that in two previously published patient groups treated with bed rest and with tranexamic acid respectively

Key words traumatic hyphaema – secondary haemorrhage – antifibrinolytic treatment.

e treatment of traumatic hyphaema has been aimed in particular at the vention of secondary haemorrhage
Ve have previously (1978) reported the results in a group of patients treated bulatory and with tranexamic acid as compared to a group of patients treated h bed rest without being able to demonstrate any statistically significant ference in the frequency of secondary haemorrhage
ince then we have treated patients with traumatic hyphaema without rest in bed principle as outpatients and without any antifibrinolytic drugs The results of a year treatment period of a relatively small number of patients are presented as h results have not previously been reported

eived July 26 1979

Material and Methods

Forty four patients were referred consecutively to the Eye Departme Odense University Hospital during the period 1/1 31/12 1978 for trea traumatic hyphaema

In cases of uncomplicated hyphaema the patients were followin, oph logical examination prescribed rest for one week as the only treatme consisted of no reading or greater physical excertion and one week s sick le work

The patients were subjected to control examination at the Eye Departme 5th and 12th days after the accident further they were given instructions t the department should a reduction in vision or pain in the eye occur Th patients below the age of 12 years were treated as ambulatory patients in ward Eleven patients with increased intraocular pressure serious lesions of bleeding within the corpus vitreum or with lesions of the retina were also a to the department and treated as ambulatory patients

The age and sex distribution of the patients are shown in Table I

Table II shows the distribution of the accompanying lesions as compared in a group of patients treated with tranexamic acid (reported in a p investigation Mortensen & Sjølie 1978) The distribution of the accom lesions in the two groups is very similar suggesting comparable severit traumas

The chi-square test with Yates correction has been employed for the s analysis and 95 % confidence limits have been used

Table I
Age and sex distribution of 44 patients with traumatic hyphaema

Age	Female	Male	Total
0– 9	1	4	5
10–19	2	13	15
20–29	1	[illegible]	8
30–39	1	[illegible]	7
40–49	0	4	4
50–59	0	[illegible]	2
60–69	0	[illegible]	3
Total	5	[illegible]	44

Table II

Accompanying lesions in 44 patients treated without tranexamic acid and 64 patients treated with tranexamic acid suffering from traumatic hyphaema

Accompanying lesions	−tranexamic acid	+tranexamic acid
Cornea and conjunctiva	25	31
Pupil and iris	27	51
Increased IOP initially	4	7
Retina and vitreus	8	13
Traumatic cataract	0	1
No accompanying lesions	7	3

Results

r of the 44 patients developed secondary haemorrhage giving a frequency of ˜ (2 5% 21 7%)

ı these four patients with secondary haemorrhage the rebleeding took place in on the first day in one on the second day and in two on the third day after the ıma

.t the final examination 43 patients had a visual acuity of ≥ 6/9 in the affected of these 3 had suffered from secondary haemorrhage

ne patient had a visual acuity of only 0 5/36 five months after the trauma A e secondary haemorrhage developed on the third day after the injury and the rse was further complicated by an increased intraocular pressure transient mochromatosis fibrinous iritis as well as corpus vitreum bleeding with perma t opacities in the corpus vitreum

Discussion

ere is little agreement as to the prognostic importance with regard to vision of ondary haemorrhage following traumatic hyphaema Neither is there agreement espect of the frequency of occurrence

ome authors (Henry 1960 Edwards & Layden 1973) thus state that the uction in visual acuity results from lesions accompanying the initial trauma itself ile others (Gregersen 1962) report that the prognosis with regard to vision is isiderably poorer following the occurrence of secondary haemorrhage Accom ıying lesions causing a reduction in vision are considerably more frequent in erican than in Scandinavian studies This would suggest a difference in the

severity of the trauma Such a difference in the composition of the ma... explain the non uniform evaluation of the importance of secondary haemorr...

Crouch & Frenkel (1976) carried out a double blind investigation o... frequency of secondary haemorrhage in 59 patients treated with bed res... aminocaproic acid or placebo Rebleeding was found in 3% of the patients ... with aminocaproic acid while 33% of the placebo group suffered from reble... A difference which was statistically significant

Bramsen (1976) found in 72 patients treated with tranexamic acid and be... one patient (1 4%) with secondary bleeding In a subsequent publication (19... rebleeding was observed in 75 patients treated ambulatory and with trane... acid

Mortensen & Sjølie (1978) found secondary haemorrhage in 5% of 56 con... tively treated patients and in 0% of 64 patients treated ambulatory and ... tranexamic acid The occurrence of secondary haemorrhage in the present inve... tion was 9 1% and statistical analysis of the three above mentioned gr... demonstrated no significant difference in the frequency of rebleeding... traumas evaluated from the accompanying lesions were not particularly sev... can be seen from Table II

Rest in bed has previously been the preferred type of treatment in the traumatic hyphaema and it has been postulated rather than demonstrated that rest has a favourable effect on the frequency of secondary haemorrhage

The results of this investigation show that the patients have been adeq... treated as ambulatory patients In our opinion there is insufficient evide... present to indicate whether or not antifibrinolytic agents should be emp... prophylactically in the treatment of traumatic hyphaema

References

Bramsen T (1976) Traumatic hyphaema treated with the antifibrinolytic drug trane... acid *Acta ophthal (Kbh) 54* 250 256

Bramsen T (1977) Traumatic hyphaema treated with the antifibrinolytic drug trane... acid II *Acta ophthal (Kbh) 55* 616-620

Crouch E R & Frenkel M (1976) Aminocaproic acid in the treatment of traumatic ... *Amer J Ophthal 81* 355 360

Edwards W C & Layden W (1973) Traumatic hyphema *Amer J Ophthal* ...

Gregersen E (1962) Traumatic hyphaema *Acta ophthal (Kbh) 40* 19 ...

Henry M M (1960) Nonperforating eye injuries with hyphema *Amer J Ophthal* ... 1298 1300

Mortensen K Kamp & Sjølie A K (1978) Secondary haemorrhage following traum... hyphaema *Acta ophthal (Kbh) 56* 763 769

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REFRACTIVE ERRORS AND OTHER OCULAR FINDINGS IN SCHOOL CHILDREN

BY

L. LAATIKAINEN and H ERKKILÄ

A series consisting of 411 non-selected school children 7 to 15 years of age was examined Decreased visual acuity (less than 0 8 in one or both eyes without correction) was found in 55 children (13 4%) the frequency increasing from 3 7% to 29 1% with age The frequency of hyperopic eyes (+2 0 D or more) decreased from 19 1% to 3 6% and the frequency of myopic eyes (−0.5 D or more) increased from 1 9% to 21 8% with age Altogether myopia hyperopia or astigmatism (1 D or more) in one or both eyes was found in 93 children (22 6%)

Manifest strabismus was found in 19 children (4 6%) and heterophoria (8 prism dioptres or more for near or distance) in 28 cases (6 8%) increasing significantly with age from 1 2 to 13 6% Amblyopia (visual acuity 0 6 or less) due to strabismus or refractive errors was found in 5 cases Subnormal vision due to congenital nystagmus unilateral macular scar congenital rubella retinopathy and unilateral Coats disease was diagnosed with one case of each Signs of external *inflammatory disease were seen in 13 cases*

In this series the annual need for ophthalmological consultation increased from 5% at the age of 7-8 to 30% of the children aged 14 15 if follow up examinations and visits for the prescribing of glasses were included

Key words refraction – refractive errors – visual acuity – strabismus – child – prevalence

ording to the 1972 law on basic health services in Finland all school children it be given regular health examinations including screening of vision No recent lemiological studies concerning the prevalence of refractive errors and other lar disorders have been carried out on Finnish school children and the annual d for ophthalmological examinations is not fully known

eived May 7 1979

Comprehensive epidemiological ophthalmological studies of school ch... been made in the USA (National Health Survey 1972) and in German(1978). In addition there are reports concerning the epidemiology of d... ocular conditions e.g. refractive errors (Goldschmidt 1968), visual acuity (... ham et al. 1978) and squint (Frandsen 1960, Rantanen & Tommila 19... populations.

The purpose of the present study was to estimate the prevalence of the ocular disorders and to ascertain the annual need for ophthalmological ... tions among school children.

Subjects and Methods

In order to obtain a representative sample of the average child popul... southern Finland the study was carried out on comprehensive school childr... all the communities in the county of Uusimaa excluding Helsinki and its ... environments. The number of children invited from each community was ... tional to the community's percentage of all the comprehensive school c... within the study area. One to three whole classes per community depend... number of children desired, were selected at random. Classes I (7-8 years), ... years), V (11-12 years) and VIII (14-15 years) were invited and were repr... by an approximately equal number of pupils. Some communities refused ... their pupils to be examined and this led to a slight inequality between ... groups.

The final sample included 23 classes. For the examination the childr... transported in small groups from the school to the out-patient depar... Helsinki University Eye Hospital. Two children who were not at school ...

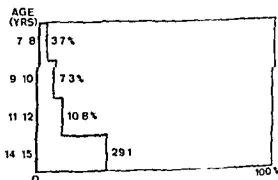


Fig. 1

Percentage of children with visual acuity of less than 0.8 in one or both eyes in the ... groups.

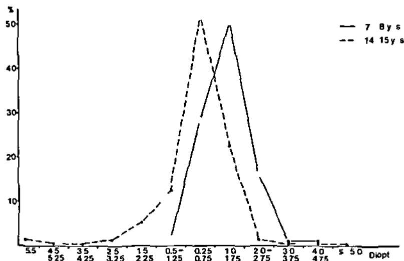


Fig 2

bution of refractive errors discovered by retinoscopy during cycloplegia and expressed
i spherical equivalents in the youngest (7 8 years) and oldest (14-15 years) age group

ie examination were excluded from the series The final sample consisted of :hildren representing the four age groups 7 8 years 81 9 10 years 109 11 12 ; 111 and 14 15 years 110 pupils

1 411 children were given a thorough ophthalmological examination including ig of visual acuity for distance with the Snellen charts streak retinoscopy both out and with cycloplegia (40-60 min after instillation of 1% cyclopentolate : in each eye) testing of eye movements and cover test followed by prism cover if phoria or tropia was detected Biomicroscopy of the anterior segment and :t and indirect ophthalmoscopy were performed in all cases

Results

al acuity

reased visual acuity (less than 0 8 in one or both eyes without correction) was nd in 55 of the 411 children (13 4%) The percentage of pupils with decreased on increased from 3 7% in Class I (7 8 years) to 29 1% in Class VIII (14 15 rs) as shown in Fig 1 In 48 of the 55 cases the visual acuity could be corrected i glasses Five eyes (1 2%) were amblyopic in two cases this was due to bismus in two to anisometropia and in one to high astigmatism In four of the : amblyopic eyes visual acuity was between 0 2 and 0 6 thus deep amblyopia

(visual acuity 0.1 or less) was found in one eye only. Other causes for de-
visual acuity were congenital nystagmus in one child and a macular chor-
scar in one child.

Refraction

A difference of one dioptre or more between the refractions measured with
with cycloplegia was found in 57 of the 411 subjects (13.9%). In the follow-
measurements obtained during cycloplegia are used.

The distribution of the refractive errors (expressed in spherical equiva-
the youngest (7–8 years) and the oldest (14–15 years) group are shown in Fig.
corresponding curves of the other two age groups, if drawn, would be bet-
these two curves. These curves reveal a general decrease in hyperopia and
emmetropia or myopia with age. Thus the percentage of moderate to
hyperopia (+2.0 D or more) decreased from 19.1% in the youngest to 3.6
oldest age group (Table I). In contrast, the percentages of myopic eyes (–0.5
more) increased from 1.9% in youngest to 21.8% in the oldest group (Table I,
a steep rise after the age of 11–12 years. The decrease in hyperopia and the in-
in myopia with advancing age were both highly significant ($P<0.0005$, χ^2
and 74.594 respectively). Astigmatic errors of 1 D. or more were found in
(1.7%) and anisometropia of more than 1 D. between the eyes was present
cases (3.6%). The percentual share of the eyes with the various refractive er-
the whole series is shown in Fig. 3. Altogether, myopia of –0.5 D. or
hyperopia of +2.0 D. or more or astigmatism of 1 D. or more in one or bot-
was found in 93 children (22.6%) and 58 (14.1%) of all the children w-
needed glasses. Glasses were usually not prescribed in monocular myopi-

Table I

Distribution of hyperopic (≧ +2.0 D.) and myopic (≧ –0.5 D.) eyes by ag-
groups

Age group (years)	Total number of eyes	Hyperopic eyes		Myopic eyes	
		No.	%	No.	%
7–8	162	31	19.1	3	1.9
9–10	218	15	6.9	14	6.4
11–12	222	26	11.7	16	[illegible]
14–15	220	8	3.6	48	21.8
Total	822	80	9.7	81	9.9

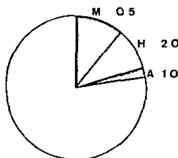


Fig 3

oportion of eyes with myopia (M $\leqq$ −0 5 D) hyperopia (H $\geqq$ +2 0 D) and astigmatism (A $\geqq$ 1 0 D) in whole series

derate hyperopia (cycloplegic refraction +3 0 D or less) wearing of glasses was sidered only if strabismus amblyopia anisometropia astigmatism or subjective iptoms related to near work were found

abismus

nifest strabismus was found in 19 of the 411 children (4 6% Table II) esotropia 12 exotropia in 7 children The prevalence of manifest strabismus showed iation between the age groups and there was no significant correlation with rancing age ($\chi^2 = 4\ 8493$ $0\ 1 < P < 0\ 2$) Twelve of the children wore glasses eight l been operated on and in three cases surgery was being considered because of large angle of deviation

Heterophoria of 8 prism dioptres or more for near or distance was found in 28 jects (6 8% Table II) esophoria in 9 (2 2%) and exophoria in 19 (4 6%) cases

Table II

Presence of strabismus by age groups

Age group (years)	Manifest strabismus		Heterophoria	
	No	%	No	%
7– 8	2	2 5	1	1 2
9–10	3	2 8	4	3 7
11–12	9	8 1	8	7 2
14–15	5	4 5	15	13 6
Total	19	4 6	28	6 8

There was a gradual increase in the frequency of heterophoria from 1.5 youngest to 13.6% in the oldest age groups which was statistically highly s ($\chi^2 = 13.761$, $P<0.005$). Four of the 9 children with esophoria wore glas because of hyperopia. The other 5 had no symptoms related to esophoria. The the 19 children with exophoria had intermittent diplopia. In 8 children of those 3 wearing of glasses was considered also because of the refractive err fusional reserves were not measured but the near point of convergence was pathological (more than 10 cm from the nose tip) only in one child who however symptomfree. One child had been operated on because of hetero At present surgery was not considered in any of them.

Other findings

Signs of external eye disease were found in 13 children: chronic blepharitis in 4 and follicular conjunctival hyperplasia in 9 cases. Only one groups had symptoms related to these findings.

In one eye Coats's disease was diagnosed and one child had rubella reti and iris hypoplasia. Twenty-two eyes (2.7%) showed diffuse coarse pigmenta the macula or the whole fundus although visual acuity was normal. Lo pigmented changes in the retina were seen in 9 eyes: grouped pigments or pigment clumping (2 eyes) or isolated pigment epithelial naevus (6 ey choroidal naevus was found in 3 eyes. Characteristics of the optic disc presented in another paper (Erkkilä & Laatikainen 1979).

Findings in 18 children with a birth weight of 2500 g or less were separately. The only finding in which they differed significantly from the others was the prevalence of manifest strabismus, which was found in 6 of the children or 33% ($\chi^2 = 35.196$, $P<0.0005$).

Discussion

Refractive errors and strabismus are the main reasons for ophthalmic consultations at school age. During childhood there is a general shift in refr towards decreased hyperopia or emmetropia, and in some eyes this chan lead to the development of myopia (Sorsby et al. 1957). From the age of 7 11–15 years this shift was found to be about one dioptre (Fig. 1); at age of peak of the curve was between +1.0 and +1.75 D, and at age of 14–15 years between +0.75 and −0.25 D.

The prevalence of myopia varies in different countries and populations in 1880 Florschütz in Germany reported that 7% of the children were myopic, whereas in the 10th class the share of myopes was

sponding age groups the frequencies of myopic eyes during the first decades is century in Finland were 1 26% and 13 6% (Heinonen 1927 1934) In the nt study the prevalence of myopia at the age of 7 8 years (1 9%) corresponded that found by Heinonen (1927) but at the age of 14 15 years the proportion of ic eyes was considerably greater (21 8%) in the present than in the earlier / (Heinonen 1934) This seems to indicate that the frequency of myopic ctive errors has increased during the last decades

e prevalence of manifest strabismus in the whole series (4 6%) corresponded that found earlier in a Finnish series of 7 8 year-old children (Rantanen & mila 1971) The frequency of heterophoria exophoria particularly increased age In most cases heterophoria was only of moderate severity and asympto- The prevalence of amblyopia (1 2%) was slightly less than that reported by anen & Tommila (1971) (1 9%) probably indicating the earlier diagnosis ection of refractive errors and treatment of strabismus

this series more than 20% of the children had refractive errors of significant ee in one or both eyes and 14% wore or needed glasses Increase in myopia the main cause for the considerable age related increase in the demand for halmological examinations At the age of 7 8 years about 5% of the children ld have been sent for ophthalmological consultation whereas the correspond figure at the age of 14 15 years would have exceeded 30% approximately the e as was also reported by Hamilton (1974) in USA On the basis of the present y it was estimated that about 15% of all school children would annually be d to need an ophthalmological examination if the follow up examinations and s for the prescription of glasses were included in the calculations However it one fifth of them might not require any treatment

References

ıla H & Laatikainen L (1979) Characteristics of optic d sc in healthy school children *ta ophthal (Kbh) 57* 914–921

schutz B (1880) Die Kurzsichtigkeit in Coburger Schulen *Jber Leist Ophthal 11* 8–449

dsen A D (1960) Occurrence of squint *Acta ophthal (Kbh)* Suppl 6?

Ischmidt E (1968) On the etiology of myopia An etiological study *Acta ophthal (Kbh) ppl 98*

ilton J E (1974) Vision anomalies of school children *Amer J Ophthal 51* 482–486

ıonen O (1927) Untersuchungen betreffend die Refraktion des Auges speziell mit rucksichtigung einiger Spezialfragen *Acta Soc Med Duodecim 9 No 3* 1–30

ıonen O (1934) Weitere Studien uber die Schulmyopie *Acta ophthal (Kbh) 12* 110–121

onal Center for Health Statistics (197?) Eye examination findings among children

United States U S National Health Survey *Vital and Health Stat ser PHS Pub* 1000 Series 11 No 115 Public Health Service Washington U S Government Printing Office

Rantanen A & Tommila V (1971) Prevalence of strabismus in Finland *Acta ophthal* 49 506–507

Sorsby A Benjamin B Davey J B Sheridan M & Tanner J M (1957) *Emmetropia and its aberrations Spec Rep Ser No 293 Med Res Council London*

Tibbenham A D Peckham C S & Gardiner P A (1978) Vision screening in children tested at 7 11 and 16 years *Brit Med J 1* 1312–1314

Toppel L (1978) Zur Epidemiologie von Augenfunktionsstörungen im Kindesalter *Klin Med 96* 1087–1094

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VISUAL SCREENING OF SCHOOL CHILDREN

BY

L. LAATIKAINEN and H ERKKILÄ

A non selected group of 411 school children 7 to 15 years of age were screened by the school nurses The screening program included (1) testing of visual acuity by the Snellen chart (with glasses if worn) (2) observing noticeable strabismus and (3) recording subjective ocular symptoms related to reading Later the whole series underwent a thorough eye examination performed by the authors including a hyperopia test and the Titmus stereo test
About 15% of the children failed to pass the screening in schools 10 0% had visual acuity of less than 0 8 in one or both eyes with glasses in another 1 0% obvious strabismus was observed and 4 1% complained of ocular symptoms The same screening procedure at the final examination revealed another 2% of children with decreased vision most of them slightly myopic
By hyperopia test 37 0% of children with cycloplegic refraction of +2 0 D or more were discovered more than half of them failed also at the present screening 2 9% of those with mild hyperopia (<+2 0 D) showed positive hyperopia test By the Titmus test all but one with manifest strabismus were discovered whereas children with mild amblyopia passed Defective stereopsis without other abnormalities was found in 11% of the children

Key words screening – visual acuity – strabismus – stereopsis – child

:ening of vision is an integral part of the regular health examinations provided school children and carried out by the school nurses In Finland visual screening sually performed in the first third fifth and eighth classes Children in other ies are also examined if ocular symptoms appear

he methods of screening and criteria for sending the children for further thalmological consultation are not uniform and their effectivity and practicabi have not been assessed In this report the results of screening by the methods

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currently used are presented and compared with those obtained by some mentary methods proposed

Subjects and Methods

This study was a part of an epidemiological investigation where the prevalence of ocular disorders and the annual need for ophthalmological examinations of school children were examined (Laatikainen & Erkkila 1980) The study consisted of school classes totalling 411 children 7 to 15 years of age described in detail in a previous paper

Before the study the school nurses were asked to examine the children by testing the visual acuity of both eyes separately for distance using the Snellen chart with and without glasses (2) observing noticeable strabismus and (3) recording subjective ocular complaints related to reading or other near work The nurses filled a form for every child including the main criterion for further ophthalmological examination whenever present The criteria given were (1) decreased visual acuity of less than 0 8 in one or both eyes (with glasses if worn) (2) obvious strabismus and (3) ocular symptoms related to near work

All 411 children were later examined by the authors at the out patient department of Helsinki University Eye Hospital After testing of visual acuity for distance without and with previous glasses a hyperopia test and the Titmus stereo test were performed in all cases The hyperopia test was regarded positive if after a short adaptation time the child was able to read correctly the Snellen figures corresponding to the visual acuity of 0 8 binocularly with +2 0 D lenses in the trial frame Cycloplegic refractions and results of the other examinations have recently been presented in detail in a previous paper (Laatikainen & Erkkila 1980)

Results

Screening of vision using the present methods and criteria

Visual acuity of less than 0 8 in one or both eyes (with previous glasses if prescribed) was found in 41 children (10 0%) by the nurses (Table 1) At the examination this criterion was found to occur in 19 cases (11 9%) Nine of these passed the same screening in schools Eight of these were slightly myopic -0 5 to 1 25 D and one was highly hyperopic +5 5 D in both eyes False positive result in the nurse s screening was found in one case only

Strabismus was the main criterion for further ophthalmological consultation in cases (1 0%) and ocular complaints related to reading or other near work in cases (4 1%)

Table I
Results of screening performed by school nurses

Criterion	Number of children	%
Visual acuity < 0 8 in one or both eyes with glasses	41	10 0
Strabismus	4	1 0
Ocular complaints related to near work	17	4 1
Total	62	15 1

Altogether the number of children who failed at the screenings was 15 17% of whole series but one fifth of them (18 6%) did not require any treatment

Hyperopia test

the whole series 54 children had hyperopia of +2 0 D or more (cycloplegic raction) in one or both eyes In 20 of them (37 0%) the hyperopia test was sitive (binocular vision for distance 0 8 or better with +2 0 D glasses) (Table II) even of the 20 were also discovered by the screening methods currently used 9 re symptom free and passed the screening A positive result in the hyperopia test s also received in 8 children with hyperopia of less than +2 0 D (2 2%)

Table II
rrelation between hyperopia (cycloplegic refraction of the more hyperopic eye) hyperopia t (binocular vision 0 8 or better with +2 0 D glasses) and present screening methods sual acuity of less than 0 8 in one or both eyes obvious strabismus or ocular complaints related to near work)

Refraction	Total number of children	Number of children with positive hyperopia test		
		Total	Failed at present screening	Passed present screening
+2 0 – +2 75 D	35	6	2	4
≥ +3 0 D	19	14	9	5
Total	54	20	11	9

Titmus stereo test

Stereoscopic acuity was poor (800 seconds of arc of disparity) in 6 child[illegible] and in 18 children (4.1%) no stereopsis was found by Titmus test. Twelve [illegible] 24 had been diagnosed and treated because of strabismus (9 cases [illegible] amblyopia (3 cases including 2 cases with organic amblyopia) (Table III). In [illegible] 24 intermittent or small angled alternating strabismus (6 cases) or anisometr[illegible] cases) was now discovered, and in 3 cases the reason for defective [illegible] remained undetected. Some decrease in stereoscopic acuity (between 800 a[illegible] seconds of arc) was found in another 57 children (13.9%). Fifteen of the[illegible] either manifest or latent strabismus (8 cases, 4 of them had earlier been t[illegible] decreased visual acuity due to anisometropia or myopia (7 cases, 3 of them [illegible] discovered), and 8 children had mild (less than +2.0 D) hyperopia w[illegible] symptoms. In 34 of the 57 cases no other abnormalities were detected.

Thirteen of the 19 children with manifest strabismus showed no or [illegible] stereopsis (≦ 800 seconds of arc), in 5 of them stereoscopic acuity was betwe[illegible] and 80 seconds of arc, and in one child it was normal. The only child with [illegible] anisometropic amblyopia showed no stereopsis, one of the 4 with mild amb[illegible] had a stereoscopic acuity between 800 and 80 seconds of arc, and in 3 of the [illegible] mild amblyopia no defect in stereopsis was discovered by the Titmus test.

Altogether in 19 cases the causative disorder for defective stereopsis had [illegible] been known and treated, and another 7 children failed at the present scree[illegible] the 10 children who had passed the present screening program interm[illegible]

Table III

Abnormalities related to defective stereoscopic acuity [illegible] by Titmus [illegible]

Stereoscopic acuity (seconds of arc)	Number of children (%)	Strabismus, anisometropia, amblyopia: Treated earlier	Untreated: Failed at present screening	Untreated: Passed present screening	[illegible]
≦ 800	24 (5.8%)	[illegible]	3	[illegible]	5
< 800 – ≦ 80	[illegible] (13.9%)	*	4	4	4
Total	81	[illegible]	*	10	4

* all passed present screening methods

all angled alternating strabismus was discovered but none of them had a metically noticeable deviation In 2 of the ten wearing of glasses due to peropia and in one case orthoptic therapy due to poor convergence was nsidered The others did not require any treatment. The number of false positive ults using the Titmus stereo test (≦ 80 seconds of arc) was 45 or 10 9% of the ole series

Discussion

ting of the visual acuity by the Snellen chart is still the basic method used in ial screening of school children although other methods to detect hyperopia or ors of binocularity have been devised (Sloane 1940 Leverett 1955 Sweeting 59 and others)

The number of children who failed to pass the present screening tests was 17% of the whole series representing the age groups from 7 to 15 years The 5-percent discrepancy in the figures of the school nurses and the authors when same screening methods were used was mainly due to the difference found in number of children with mild myopia indicating either too short a distance used the examination of the visual acuity in schools or just the peering of children ween half-closed lids About one fifth of the children who failed at the screening ts did not require any treatment.

Half of the children (9/19) with moderate hyperopia (cycloplegic refraction +3 0 or more in one or both eyes) failed to pass the present screening due to reased visual acuity strabismus or subjective ocular complaints One quarter re (5/19) would have been detected by the hyperopia test (Table II) for two of se five glasses were prescribed Wearing of glasses was not considered in oderate hyperopia without other abnormalities strabismus amblyopia anisome pia or astigmatism unless subjective symptoms related to reading or other near rk were present. Another quarter (5/19) of hyperopic children remained detected by the hyperopia test. The value of the hyperopia test particularly after age of 8 9 years has been pointed out by Sloane (1940) and Yasuna & Green 52) In this series the use of the hyperopia test would not have added much to present screening results

In this study the number of amblyopic children was so small that the value of the tmus stereo test in screening of amblyopia could not be assessed However in 3 t of 4 children mild amblyopia would not have been discovered by the Titmus t The shortcomings of the Titmus test in amblyopia screening have also been ported by Simons & Reinecke (1974) and Walraven (1975) although the latter thor stated that in his study on children aged 2 to 7 years the poor performance

of the Titmus test was almost entirely due to its inadequacy for use with 4 year-old children. In the present study the other stereo tests were not used.

Intermittent and small angled alternating strabismus were seldom detected by the present screening methods but all these cases except one were detected by the Titmus stereo test. In this respect a stereo test would have been a useful supplement to the present methods but the great number of false positives by the Titmus test reduces its value as a screening method. Most of the children with small angled alternating strabismus detected by the Titmus test did not require treatment because there was no cosmetically noticeable deviation. For vocational guidance the diagnosis of defective stereopsis would have been valuable.

The onset of most visual abnormalities like strabismus (Nordlöw 19[illegible]) and refractive errors occurs before school age and they should also be treated in order to prevent permanent amblyopia or difficulties and delays in the child's performance. Screening for amblyopia should therefore be done at the preschool age as has been advised by Allen (1957, 1967), Kaivonen & Koskenoja [illegible] Lippmann (1969), Rosenthal & von Noorden (1971), Tommila (1976) and [illegible]. Developing myopia, moderate astigmatism and high hyperopia are [illegible] decrease in visual acuity. Other refractive errors or slight abnormal [illegible] motility seldom need treatment unless subjective symptoms or cosmetic[illegible] able defects are present. Therefore, after proper screening at the preschool age, the methods currently used for screening of school children seem to be [illegible].

References

Allen H. F. (1957) Testing of visual acuity in preschool children. Norms, variables and a new picture test. *Pediatrics 19* 1093–1100

Allen H. F. (1967) Incidence of amblyopia, editorial. *Arch. Ophthal. (Chicago)* [illegible]

Kaivonen M. & Koskenoja M. (19[illegible]) Visual screening for children and [illegible] preliminary experience from its application in practice. *Acta ophthal. (Kbh.)* [illegible]

Laatikainen L. & Erkkilä H. (1980) Refractive errors and other ocular findings in school children. *Acta ophthal. (Kbh.) 58* 129–136

Leverett H. M. (1957) A school vision health study in Danbury, Connecticut. *Amer. J. [illegible] 39* 527–540

Lippmann O. (1969) Vision of young children. *Arch. Ophthal. (Chicago) 81* [illegible]

Nordlöw W. (19[illegible]) Squint – the frequency of onset at different ages and the incidence of some associated defects in a Swedish population. *Acta ophthal. (Kbh.) 42* [illegible]

Rosenthal A. R. & von Noorden G. K. (1971) Clinical findings and therapy in [illegible] myopia associated with amblyopia. *Amer. J. Ophthal. 71* [illegible]

Simons K. & Reinecke R. D. (1974) A reconsideration of amblyopia screening [illegible] *Amer. J. Ophthal. 78* 707–713

...ane A E (1940) Massachusetts vision test An improved method of testing eyes of school children Arch. Ophthal (Chicago) 24 924 939
...eting O J (1959) An improved vision screening program for the New Haven schools J Amer Optom. Ass 30 715-722
...nmila V (1976) Vision screening in preschool children (In Swedish) Finska Lakare sällskapets Handlingar 136 76-81
...raven J (1975) Amblyopia screening with random-dot stereo-grams Amer J Ophthal 80 ...93 900
...una E R. & Green L S (1952) An evaluation of the Massachusetts vision test for visual screening of school children Amer J Ophthal 35 235-240

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CYSTICERCUS CELLULOSAE IN THE LACRIMAL GLAND ORBIT AND EYE LID

BY

DHAN KRISHNA SEN

Six cases of adnexal cysticercosis (1 in the lacrimal gland 3 orbital and [illegible] palpebral) have been reported. In the lacrimal gland it presented as a [illegible] translucent cyst which closely simulated a simple dacryops. In the orbit [illegible] the cases presented as an acute abscess in the upper and inner [illegible] However one of them initially presented and existed as a case of simple [illegible] for a period of 8 months. The third orbital case appeared as a painless [illegible] the upper and outer quadrant. In the lid the larva presented as a subcutaneous nodule in one case and in the other it was lodged in the orbicularis [illegible] muscle. The cyst was surgically removed in all cases and the diagnosis was confirmed by histopathological examination. Lodgement of cysticercus [illegible] the lacrimal gland and in the orbicularis oculi muscle is reported for the first time.

Key words: Cysticercosis – orbital abscess – proptosis – ptosis – lacrimal cyst [illegible] nodule – adnexal lesions – orbital cyst

Cysticercus cellulosae the larval form of Taenia Solium can get lodged [illegible] the ocular tissues but its lodgement in the ocular adnexa is considered [illegible] even in countries where ocular cysticercosis is still common.

The present paper reports 6 cases of adnexal cysticercosis seen [illegible] department of L.N.J.P.N. Hospital New Delhi in details. The break up of [illegible] of lodgement is lacrimal gland (1) orbit (3) and lid (2).

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Case Reports

A 14 year-old girl reported with the history of occasional discomfort in the left eye for nonths During examination of the eye a translucent smooth cystic swelling about the f a pea was seen in the palpebral portion of the lacrimal gland The overlying ıctiva and the surrounding tissues appeared normal The cyst was painless on pressure osely simulated a simple dacryops The eye ball itself was normal Ocular rotations were ıd also painless There was no history of trauma to the region The cyst was excised etely Histological appearance of the cyst was typical of a cysticercus cyst (Fig 1)

! An 8 year old boy reported with progressive drooping of the left upper eye l d for ear Detailed ophthalmic general physical and neurological examinations revealed no abnormality All special investigations were negative Repeat ophthalmic and medical ups at periodic intervals were noncontributory After 8 months the child was brought evere pain and swelling in the left eye and fever for 2 days On examination the left eye as proptosed and displaced downwards and outwards There was oedema of the lids edish discolouration of the skin on which distended veins could be seen (Fig 2) Ocular ments were grossly limited The globe itself was normal A diagnosis of acute orbital itis was made The cause of cellulitis could not be ascertained Nose and paranasal es were clinically and radiologically normal The child was treated with broad spectrum iotic and steroid systemically and other supportive measures but suppuration eventually ved The pus found its way forwards and presented under the conjunctival fornix in the r nasal quadrant A free incision was made into the abscess and during drainage a samll



Fig 1

histological appearance of the cyst removed from the palpebral part of the lacrimal d in case 1 showing the body of the larva cysticercus cellulosae The membrane around : central cavity shows typical gland shaped convolut ons (Haematoxylin and eosin X 25)



Fig 2

Case 2 showing marked forward downward and outward displacement of the ... oedema of the lids with distended veins on the skin on the left side

translucent cyst with a white spot on its surface escaped along with pus. On cul... was sterile. The boy recovered with minimal ptosis and some limitation of ocular ... in looking up and in

Case 3 A 6-year-old boy presented with acute orbital abscess in the upper inner ... the left side with signs of optic neuritis. The fundus was normal. During dra... a typical cysticercus cyst escaped. With full doses of broad spectrum antibio... systemically the child recovered without any ocular disability

Case 4 A 16 year-old girl reported for an eye check up. During examination a ... mm × 7 mm was discovered in the upper outer quadrant of the left orbit. There ... of inflammation around the cyst. The globe was not displaced. Ocular mo... cyst was completely excised

Case 5 A 5 year-old boy was brought with a painless subcutaneous nodule ... situated just below the middle of left eye brow. It was first noticed 3 months previo... noudle was excised

Case 6 A 10-year-old boy accidentally discovered a painless small hard ... mm while passing fingers over the closed left upper lid ... examination it was somewhat mobile under the skin but its mobility was greatly ... the lids were tightly closed. On surgical exposure the nodule was found ... fibres of the orbicularis oculi muscle. It was completely excised

None of the cases gave any history of eating pork. A complete general ... examination and multiple tests demonstrated no other foci of cysticer... same eye in the other eye or any where else in the body in any of the cases ... was surgically removed in all the 6 cases and the diagnosis was established ... them by histopathological examination

Comments

• case with a cysticercus lodged in the lacrimal gland appears to be the first to be orted in the literature It presented in the form of a painless translucent cyst, ch was misdiagnosed clinically as a simple dacryops

ysticercosis of the orbit is relatively rare Out of 372 cases of ophthalmic ction by such cysts recorded in the literature only 19 were found in the orbit isgien 1911) and since then references on orbital cysticercosis have been eptional The site of lodgement of a cysticercus cyst is near the orbital margin l only very rarely in the depths of the orbit (Duke Elder 1974) It is of isiderable clinical interest to note that a cysticercus was lodged in the depth of the it in 2 of the 3 orbital cases reported here The sequence of events in one of m was unique in that it presented and existed as a case of simple ptosis for which cause could be established for eight months in spite of repeated medical and irological check ups and extensie investigations

Cysticercosis of the lid is exceptional (Duke Elder 1974) In recent world rature only one case has been recorded (Jampol et al 1973) In all cases of lid ticercosis so far recorded the cyst was found to be lodged in the subcutaneous ue One of our lid cases appears to be the first where a cysticercus was found lged in the orbicularis oculi muscle

The cases recorded here illustrate thet the presentation of adnexal cysticercosis is ned and the condition therefore should be considered in the differential gnosis of all adnexal lesions in patients from areas where Taenia Solium is evalent

References

ike Elder S (1974) *System of ophthalmology* Vol 13 Part I p 19, and part II p 929–930 Henry Kimpton London

mpol L M Caldwell J B H et Albert D M (1973) Cysticercus cellulosae in the eye lid *Arch Ophthal (Chicago)* 89 319–320

isgien (1911) Cited by Duke Elder S (1974)

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Table I

Summarizing the clinical manifestations in the affected members of the C family

Patient	III 1	III 2	III 6	III 7	III 9	II 3
Age (years)	31	26	16	14	9	50
Sex	m	m	f	f	f	f
Mean spherical error	−18	−7 75	+0 25	+0 25	−2 75	+2 00
Mean astigmatism	?	2 50D	1 75D	1 50D	1 00D	2 50D
Visual acuity	no light sense	6/24 6/60	6 60 6/24	6 60 6 60	6/12 6/36	6/60 6/9
Macular Change	?	foveal cyst	degeneration	degeneration	foveal cysts	pigment mottling
Peripheral preretinal membrane	detachment	360	270°	270°	−	−
Pigmentary degeneration	?	+	+	+	−	+
Optic atrophy	?	+	+	+	+	+
Inversion of disc vessels		+	+	−	−	+
Vitreous degeneration		+	−	−	(+)	+
Complicated cataract	+	+	−	+	−	+
EOG	?	night blind	flat	?	?	?
ERG	?	night blind	flat	?	normal	flat
Field constriction		+	+	?	?	+
Squint	ny tagm	−	−	lt gent	e s nt	l e gent

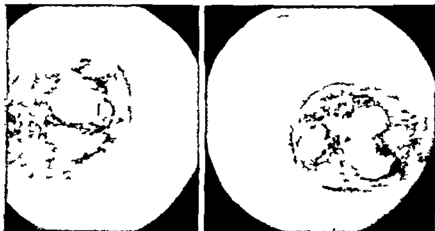


Fig 2
and left maculae in 16 year old girl (III 6) who also has peripheral vitreous hments In the central cystic parts the choriocapillaris and most of the pigment elium are absent The large choroidal vessels are only covered by a thin pellucid slightly ented membrane In the peripheral parts there is heavy pigment epithelium dystrophy ing the choriocapillaris The demarcation towards the periphery is by an annular edematous zone

macular lesions Two types of macular lesions are found in the family members 26 year-old propositus has a single cyst in the right fovea and his 9 year-old r has 5 6 small confluent cysts in both foveae with slight change of the macular nent epithelium A severe bilateral macular destruction is seen in two sisters 16 14 years-old The lesions are two to three disc diameters wide sharply iarcated and covered by a continuous membrane which is flush with the ounding retina The central part one to two disc diameters wide is cystic due to absence of the choriocapillaris and most of the pigment epithelium The large roidal vessels and the sclera are covered by a thin pellucid outer membrane and osed to view through the glossy central windov s" in the inner membrane vards the periphery there is pigment epithelium dystrophy with pigment umulations and depigmentations in some places unmasking the underlying ophic choriocapillaris Rarely a retinal vessel crosses the border of the lesion The narcation towards normal retina is by an annular edematous zone

he mother of the siblings has macular pigmentary mottling but there is no cyst mation

ipheral preretinal membranes Peripheral preretinal membranes are present in ee patients The membranes were first observed in the temporal periphery in

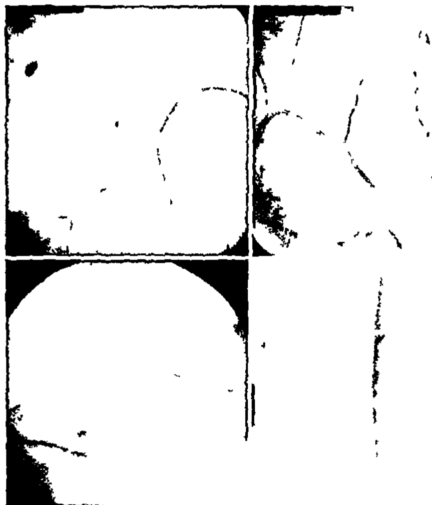


Fig 3

Fig 3a and b show upper temporal preretinal membranes in left and right eyes in 91 male The demarcation line is seen tangentially and appears sharp In a there is condensation of the membrane In "b the lesion has extended across photoc marks Localized periphlebitis is seen in central vessels Fig 3c Ballooning membrane at 1 o clock in right eye of 16-year-old girl Cryopexy has been applied Nasal periphery of left eye of the same patient showing high preretinal mem stretch creases

front of the equator and gradually extended posteriorly and ce encompass most or all of the periphery In two sisters 16 and 14 years membranes originate from the oral region and extend posteriorly to or at equator They are ballooning forwards and in one eye actually showing creases on the surface They are avascular and pellucid but dense eno

'd l) seen \ ith the b nocular ind rect ophthalmoscope Small condensations are
ı n the tri mirror lens The posterior attachment of the membrane to the ret na
ces a sharp l ne although small condensed tongues sometimes stretch further
teriorl) In the 26-year-old propos tus the preretinal membrane has collapsed
ıg most of the circumference and now presents as a curled up gre ısh wh te
d near the equator barel) \is ble in parts the membrane be ng only preserved
\e temporally

vitreo is bod) Degeneration of the \itreous is evident in three pat ents Two
ents have anterior vitreous detachment and anterior f brillar degeneration and
eres s with format on of a few \ertical strands In another patient the vitreous
nge is less marked with some l quefact on and some syneres s The two sisters
ı extens \e preretinal membranes apparently have a normal vitreous gel

mentary degeneration Apart from the macular lesions p gmentary change is found
v in the equatorial region where p gment clumps or a un form dense hyperp g
ntat on may be found in the latter case giving a dense brownish apperance

pap llae All the affected fam ly members have a un form d sc pallor and in
ee pat ents there is invers on of the d sc \essels The retinal \essels generally
pear normal apart from occas onal localized th nn ng and per phlebit s n two
ents

lens Three s bl ngs and the r mother have complicated cataracts n the form of
e posterior subcapsular opacities arranged in a stellate fash on The oldest blind
other has dense cataracts on both s des

ract on and vis al act ty All patients ha e an astigmatism ranging between one
d three d optres and the mean spherical error ranges between +2 D and −18
, see Table I

ctrooc ular tests Electroretinograms were recorded in three of the patients In two
es the a and b-waves were ext ngu shed under photop c and scotop c cond t ons
ereas it was normal in one affected pat ent An electrooculogram was only
orded in one case and showed no l ght rise One affected patient who was not
amined has been complaining of increas ng d fficulty w th n ght \is on for a few
ars



Fig 1
Fluorescein angi grams of right n acula in 16 year-ol l gi l Early p cture and 10 m n N te l yperfluorescence in tl e peripl eral parts of tl e lesion n the late p cture Al retent on c f fluorescein in the demarcat n zor e corresp n l ng w l tl e annula ede
Fig 2

The visual fiel ls When recordable the visual fields in the affected pat ents s concentric peripheral constriction to around 20° with a large wh te object I patient with large macular lesions a corresponding central scotoma demonstrated

Motility disorlers Two patients have divergent squints and one ch ld has convergent squint Two siblings one of whom without l ght percept on h horizontal undulating nystagmus

Fl iorescein angiograms were done in three affected pat ents In the propositus has a macular cyst they show normal masking of the macular choro d and the no dye leak In his mother who has macular pigment change but no cro oedema the 10 min pictures show diffuse choro dal hyperfluorescence fovea In his 16-year-old sister the late pictures sho hyperfluorescence peripheral part of the characteristic lesions and in the demarcation zone cor ponding with the annular oedema

General symptoms One patient is severely mentally deficient with an I Q of 56 T of his sisters are mentally retarded and suffer from spast c hem plegia Furth more one of these girls and her mother have hypacusis

Discussion

r of the six patients included in the material have peripheral preretinal nbranes and/or macular lesions One patient with high myopia developed teral retinal detachments in his late teens It is likely that the etiology for his ichments is the genetic defect apparent in some of his siblings more especially seems that patients with bilateral juvenile retinal detachments are likely to have treo-retinal degeneration (Francois et al 1974) The mother although having her central cysts nor peripheral preretinal membranes displays all the side nifestations of the disease and so probably carries the abnormal gene There is report of poor eyesight in her family which would not exclude the disease in a d form however Her husband has normal visual acuity and no vitreous change etinal degeneration in spite of high myopia

ith two subsequent generations and five siblengs out of a sibship of nine being cted the likely mode of transmission is by a single dominant gene with varied ression A slight possibility would be an autosomal recessive transmission with a tial penetration in the carrier state whereas a recessive x linked transmission is d out by the fact that both girls and boys carry the disease

he outstanding signs of the present disorder are the macular lesions and the retinal membranes The macular change is seen through several degrees in the cted family members Three stages can be defined 1) Early pigmentary change h small pigment granules and depigmentations in the macula observed in one of affected girls from the age of three years 2) Formation of foveal cysts with a served choriocapillaris in two of the patients starting around the age of six rs 3) Degeneration of pigment epithelium choroid and probably retina with formation of a large macular cyst cavity

he peripheral membranes have only been noticed from an age of eleven years bably because the patients are difficult to examine The shape of the membrane the two girls suggests a retinal splitting in which case the inner leaf would be de up of the thickened basal lamina of the retina However the fact that the inal vessels in all cases remain at normal retinal level makes it more likely that the mbranes are actually thickened posterior vitreous membranes formed after reous detachment At the same time there is probably degeneration of the ripheral retina as evidenced by the visual field constriction The extinguished G suggests a defect in the receptor cells as well as in the Muller cells

Differential diagnosis

gner s hereditary vitreo retinal degeneration In this dominant condition the vitreous ays shows fibrillar degeneration and a peripheral avascular band or line of Vogt

along the equator A number of investigators have found a very f membrane stretching forwards from the equator towards the oral region (1938 Jansen 1962 Alexander & Shea 1965) Hirose et al (1973) demonstrate fusion anteriorly between the membrane and the a of the degenerate vitreous They found the vitreous detached both in front of behind the "grey line" The general consensus is that the membranes Bohringer et al (1960) on section of post mortem eyes of the original Wa family found a membrane attached to the inner limiting membrane of the r while Ricci (1969) on other sections of the same eyes demonstrated retinal in the nerve fibre layer and macrocystic degeneration of the periphera Other characteristics of Wagner s disease are localized choroidal strands of fibrosis and pigmentations (Alexander & Shea (1965) Jansen (1962) macula is always normal Visual reduction is mainly caused by complicated cat which requires extraction in the third or fourth decade There is contraction of visual fields and optic atrophy is common

The vitreo tapeto-retinal degeneration of Goldmann Favre In this rare autoso recessive condition the patients have early reduction of visual acuity hemeralopia from early childhood The morphological characteristics are ma macrocysts formed by confluence of small cysts and peripheral retinoschisis in the lower temporal quadrant Scattered pigmentation sometimes of b corpuscular appearance and strands of choroidal atrophy are common. The microfibrillar vitreous degeneration and complicated cataract The ERG is ex uished in more advanced cases

In *the x linked juvenile retinoschisis* a macular retinoschisis is always present, a lower temporal vascular retinoschisis is common Other characteristics are va veils protruding into the vitreous localized perivascular sheathings lattice de ration and scattered pigment clumps Vitreous degeneration is found in s cases Optic atrophy and inversion of the disc vessels occurs The ERG b-wa reduced also when there is no peripheral retinoschisis

The two latter diseases differ from the family condition in question partic in having peripheral retinoschises carrying retinal vessels The other retinal s the two diseases are also absent The differential diagnosis from Wagner s d more difficult especially in the propositus who has equatorial bands vit degeneration and cataract but who does not manifest the other Wagner charg the posterior poles His two sisters are clearly distinguished by the impr macular degeneration which has never been described in Wagner cases or in any of the vitreo retinal degenerations

seems then that the family condition in question takes its place among the ·o-retinal degenerations although it cannot be classified into any of the three ı groups

Acknowledgements

ıks to Dr C T Millar for doing the electrophysiologig tests to Mr R C Hood for doing : of the fundus photographs and to the W H Ross Foundation (Scotland) for the Study ·evention of Blindness for economic support

References

ander R. L. & Shea M (1965) Wagner s Disease *Arch Ophthal Chicago 74* 310–318

ringer H R Dieterle P & Landolt E (1960) Zur Klinik und Pathologie der degeneratio 'aloideoretinalis hereditaria (Wagner) *Ophthalmologica 139* 330–338

s P A (1965) Retinoschisis Retinal Cysts *Trans. amer Ophthal Soc 63* 417–453

e M (1958) A propos de deux cas de degenerescence hyaloideoretinienne *phthalmologica 135* 604–609

r-Ofry V Adam A Regenbogen L Godel V & Stein R. (1969) Hereditary itreoretinal Degeneration and Night Blindness *Amer J ophthal 67* 553–558

e C & Ricci A (1976) La degenerescence hyaloideo-tapeto-retinienne de Goldmann ivre *Arch Ophtal. (Paris) 36* 127–136

icois J De Rouck A & Gambie E. (1974) Degenerescence hyaloideo-tapeto-retinienne de oldmann Favre *Ophthalmologica 168* 81–96

idsen E (1966) Hereditary Hyaloideoretinal Degeneration (Wagner) in a Danish Family *'ta ophthal. (Kbh) 44* 223–232

ose T King Y L & Schepens C L (1973) Wagner's Hereditary Vitreoretinal egeneration and Retinal Detachment *A ch Ophthal. Ch cago 89* 176–185

en L M A A (1962) Degeneratio Hyaloideo-Retinalis Hereditaria. *Ophthalmologica 144* 58–464

bloch W H (1975) Inherited Hyaloideoretinopathy and Skeletal Dysplasia *Trans amer phthal Soc 73* 417–451

is R A Lee G B Martonyi C L Barnett J M & Falls H F (1977) Familial foveal etinoschisis *Arch Ophthal. Chicago 95* 1190–1196

in I & MacRae A (1938) Congenital Vascular Veils in the Vitreous *Brit. J Ophthal 22* –10

'icar J E. & Wilbrandt H R. (1970) Hereditary Retino-schisis and Early Hemeralopia *rch Ophthal. Chicago 83* 679–636

ı A (1969) Classification des degenerescences vitreo-retiniennes en relation avec le ecollement de retine *Probl actuels ophtal. 8* 183–905

sby A Klein N Gann J H & Siggins C (1951) Unusual Retinal Detachment possibly ex Linked *Brit J Ophthal 35* 1–19

gner H (1938) Ein bißher unbekanntes Erbleiden des Auges (Degeneratio hyaloideore inalis hereditaria) beobachtet im Kanton Zurich *Kl n Mbl. Augenheilk. 100* 840–857

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S A *Hassani* Real time ophthalmic ultrasonography Springer Verlag New York F berg *Berlin 1978 214* pages 423 illustrations and accompanying text and index

This book deals with the principles of ultrasonography and in particular ultrasonography in the evaluation of eye diseases

The book is divided into the following sections Principles of ultrasonography anatomy sonoanatomy ultrasonic patient history and oculosonotomography These give an excellent introduction to ultrasonography

After this the ultrasonographic findings in eye diseases are presented in the sections Sonography of the injured eye lens vitreous retina and choroid, optic nerve, ophthalmic tumors and sonography of the eye in systemic disease To each section there abundance of illustrations of high photographic quality The accompanying text is The last section deals with artifacts in ultrasonic investigation

The book is instructive and can be recommended for practicing ophthalmologists those dealing with ultrasonography

Th thal B

C Kommerell Augenbewegungsstorungen Neurophysiologie und Klinik (Disorders of motility neurophysiological and clinical aspects) Symposion der Deutschen Ophthalmologischen Gesellschaft von 15 – 17 April 1977 in Freiburg J F Bergmann Munchen 1978 386 pages including table of contents subject index references many figures and pictures in black/white Price per Fascicle DM 90 –

The subjects of the symposium comprise the structure the function and the innervation the eye muscles e g how this sensomotoric reflex pathway is affected by squint operations *One of the other main topics of the meeting is focal* diagnosis

The first chapter of the book contains studies on the morphology of the eye motor units metabolism insertion and the connective tissue apparatus Then about the peripheral oculomotoric system (a survey slow eye movements and dynamic power) After a chapter about electromyography there is a chapter concerning studies various aspects of muscular surgery (comparisons between theoretical and clinical vertical strabismus caused by horizontal muscles changes of the saccade velocity muscle surgery consecutive divergent strabismus etc) The second half of the book among other things 13 lectures on the supranuclear organisation of the ocular differential diagnostic considerations in patients with disturbances of gaze combined motility defects Then follows a chapter with works on cyclo further chapter on cerebellar motility disturbances and associated differential problems The last part of the book contains lectures on among other topics nystagmus fixation disturbances and on normal and abnormal fusion movements

The contents of the book/the meeting are thus made up of works from neurophysiologists neurologists and ophthalmologists who all belong to the elite each in his own expert domaine The drawing up of the congress report pictures figures and tables is perfect In spite of the shape of proceedings possible to give the book a quality of unity thus making it comprehensive with and much new knowledge amongst the over 0 lectures/articles

F C

odal W Hild J van Limborgh R Ortmann T H Sch ebler G Töndury and E Wolff Advances in Anatomy Embryology and Cell Biology Vol 54 Part 4 Vogel M Postnatal Development of the Cat s Retina 1978 Springer Verlag Berlin Heidelberg New York 66 pages 27 figures 2 tables Price soft cover DM 33 – US dollars 16 50

present study is a light and electron microscopical examination of the retinal develop- of the cat both qualitatively and quantitatively Altogeter 17 cats have been examined six hours after birth until adult age with the shortest intervals from the first days after The retinal area examined was temporal to the optic disc

: first half of the study deals with the results of the qualitative morphological ination and here the development of the individual retinal layers and their individual ures are illustrated with excellent relevant electromicroscopical photomicrographs il attention is given to the problem concerning the genesis of the photolamellas the onship between the pigment epithelium and the receptors and morphogenetic cell

he second section the quantitative results are discussed comprising both the volumetric inations of the retinal structures where the point counting technique is used together he examination of the thickness of the individual retinal layers at the different stages of opment

e examination concludes that the individual retinal structures have chronologically ent phases of differentiation and for the retina as a whole there are three stages of opment namely an initial phase during the first postnatal week a main phase from the if the first week until 30 days after birth and a differentiations phase from 30 days until nonths postnatally

the whole the examination results with demonstration of the centripetal maturation of tinal structures correspond to previous examination results

e study can be recommended to anyone interested in electronmicroscopy of the retina ts development

K E Rasmussen

Krieg lstein and W Leydh cker Glaucoma update International Symposium Nara Japan May 7–11 1978 Springer Verlag Berlin Heidelberg New York ISBN 3540093508 224 pages 48 figures 27 tables Price DM 48 – US dollars 26 40

not hesitate to advise all ophthalmologists to read the symposium to which various oma specialists have contributed It gives us an impression of the enormous efforts both rimental and mental displayed within this field We must admit howe er that none of umerous studies have succeeded radically in giving us the weapon required to definitely ce the incidence of the tragical blindness due to senile glaucoma

ie ophthalmic medical practitioner must know the truths regarding glaucoma and ve instructions concerning treatment

ie operating ophthalmologist must admit that no really satisfactory procedure exists as

e cannot prevent glaucoma induced blindness having no adequate control of th s disease ate But we can learn to do our best

this book we can read about the enormous efforts displayed to solve the problems and at ame time about our insufficiency

P B andstr p

C M Bleeker et al Proceedings of the 3rd International Symposium on Orbital Disor Amsterdam September 5–7 1977 Dr W Junk by Publishers The Hague & London 1978 Price Dutch Guilders 175 – US dollars 87 50

The 3rd International Symposium on Orbital Disorders took place in Amsterdam September 1977 The proceedings from this symposium are compiled in this excellent comprising 546 pages which deal with practically all aspects concerning the orbit and different diseases that can be found in this small area

During the last few years rapid progress has been made in the development of techniques of examination and the treatment of the diseases of the orbit, and the reader the articles of this book not only gets an impression of the present possibilities, but obtains a critical evaluation of these possibilities The development of CAT-scanning especially been revolutionary and has added new dimensions to the diagnosis of the dis of the orbit and our knowledge of the anatomy of the orbit Several articles in the book concerned with CAT scanning but there are also articles about other methods of exam tion such as ultrasound phlebography and arteriografy Several articles compar diagnostic value of these different methods of examination

The diseases of orbit – inflammations tumors endocrine and vascular diseases naturally all treated and discussed in several articles One advane here was the importance Thyrotropine releasing hormon TRH in the diagnosis of endocrine ophthalmoplegia

Orbital surgery is also discussed in this symposium and there are articles about both lat and medial decompression and reparative surgery is also represented

The work the 3rd International Symposium on Orbital Disorders is especially relevant the ophthalmologist neurosurgeon or otologist who is concerned with the treatment of diseases of the orbit The book is excellent and can be warmly recommended

S Fanrd

H J Kuchle and H Busse Taschenbuch der Augenheilkunde Verlag Hans Huber & Stuttgart Wien 1978 Price DM 68 –

The second edition of Kuchle and Busse s Taschenbuch der Augenheilkunde is a well wr book comprising 408 pages in which the 1st edition from 1965 has been brought up-to-d with regard to diagnosis and treatment The content – divided into 28 chapters is ju extensive and adequate as that of the best ophthalmological textbook and are illustrated relevant photographs (six of these pages are in colour) drawings diagrams and schems can be discussed whether or not it is reasonable in a pocket book to include e g dra the emmetropic myopic and hypermetropic eye and ophthalmodynometry but in the the book is also useful for those non-ophthalmologists with an interest in ophthalmolo topics The authors have managed to get much material into pocket book form partly bec the language is short and concise and partly because the book is in small print At the bac the book there is a valuable survey of the most common ophthalmological syndromes.

Apart from the fact that the contents are quite adequate for a pocket book and a boo reference of this type the excellent binding and the quality of the paper make it abel useful as such and it can therefore be recommended to anyone needing to be rap orientated in ophthalmological problems when the opportunity for consulting the b works is not available

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CELL MEDIATED IMMUNITY TO HERPES VIRUS TYPE 1 PATIENTS WITH RECURRENT CORNEAL HERPES SIMPLEX

BY

HELGA HAMMER and ATTILA DOBOZY

The proportion of T lymphocytes in the peripheral blood their phytohae magglutinin reactivity and the leycocyte migration inhibitory effect of purified tuberculin protein were found to be equal in 25 recurrent corneal herpes simplex patients and 17 healthy individuals who had never suffered from clinically manifest herpes simplex virus (HSV) infection Conversely the HSV vaccine inhibited the leucocyte migration in the healthy group but not in the recurrent herpes patients when the clinical symptoms were manifest In 14 recurrent corneal herpes simplex patients the examinations were repeated after a 3 month symptom free period and in these periods the patients corresponded equally to the healthy group in every respect

Key words herpes simplex virus – corneal herpes – cell mediated immunity

ıes simplex virus (HSV) is a frequent causative agent of recurrent eye disease pathology of the primary corneal herpes simplex is well known however many ıons regarding recurrences remain unsolved Thus the role of immunologic ıllance in the precipitation and healing of recurrent herpes simplex is ıown

spite of the fact that the host defence against virus infections is governed by nediated immunity only a few investigations of the cellular immune defence in infections have been performed and the results of the lymphocyte transforma the lymphokine synthesis and the direct lymphocyte cytotoxicity were contradic (Rosenberg et al 1974 Russel 1973 Starr et al 1975 Thong et al 1975 ɔn et al 1972)

ı the present work the T lymphocyte system in general and the specific mediated immunity against HSV type 1 in patients suffering from recurrent

ıved May 16 1979

corneal herpes simplex in the active phase of the disease and in the symptom free interval and of healthy individuals without any history of manifest HSV infection were compared. To estimate the T lymphocyte system in general the proportion of E rosette forming cells (T lymphocytes) in the peripheral blood, their phytohaemagglutinin (PHA)-reactivity and the leucocyte migration inhibition by purified tuberculin protein (PPD) were determined. The specific cellular immunity against HSV was also investigated by means of a leucocyte migration test using HSV antigen.

Material and Methods

Patients. Studies were performed on 25 patients suffering from recurrent herpes simplex (17 males, 8 females, average age 37 years) in whom recurrence had occurred at least 3 (maximum 7) times. Examinations were carried out in the active phase of the disease and were repeated in 14 patients after a symptom free period. The data thus obtained were compared with the normal ones for 17 healthy individuals (11 males, 6 females, average age 31 years) who never suffered from recurrent herpes.

E rosette counting was performed according to the method of Lay et al. (19..) with some modifications. 1.5×10^5 lymphocytes and 5×10^6 washed sheep erythrocytes were taken in a volume of 0.1 ml Hanks solution and 0.05 ml calf serum added. The cell suspension was centrifuged (3 min, 400 g, 18° C) and incubated for 2 h at 4° C. Subsequently the sediment was suspended by rotation and the proportion of rosette forming lymphocytes was determined. Three sheep erythrocytes were taken as a minimum to define the rosettes.

The leucocyte migration test and the method of phytohaemagglutinin stimulation of lymphocytes have been described previously (Hammer 1971, 1974). In the leucocyte migration tests PPD and HSV type I vaccine (Lupidon® produced by Hermal, Hamburg) respectively were used as antigens. The extent of migration inhibition was expressed by the migration index, which is the ratio of migrations of cultures containing the respective antigen of the controls. A migration index lower than ... was evaluated as positive. The PHA reactivity was estimated from the increase of ^{3}H thymidine incorportion (cpm/10^6 lymphocytes).

Results

There was almost complete agreement between the general activity of the lymphocyte system of healthy individuals and of the patients with recurrent

-s simplex the proportion of E rosette forming cells (T lymphocytes) their reactivity and the leucocyte migration inhibitory effect of PPD (Table I) were to be equal In contrast to this the HSV type 1 vaccine inhibited the yte migration in the healthy individuals but not in the recurrent corneal s simplex patients in the manifest period the average migration index was cantly lower for the healthy individuals than for the recurrent herpes simplex ts ($P < 0\ 01$)

4 recurrent corneal herpes simplex patients the leucocyte migration inhibi ffect of the HSV vaccine was reexamined after a symptom free period of ths duration In 13 of the 14 patients this antigen resulted in a higher tion inhibition (lower migration index) in the symptom free period than in ge when clinical symptoms were manifest (Table II) The difference between igration indices averaged for the active phase of the disease and for the om free state is statistically significant ($P < 0\ 01$)

Discussion

ast 15 years have witnessed a transition from the purely serological to the comprehensive immunological aspects of HSV infections

Table I

roportion of T lymphocytes in the peripheral blood their phytohaemagglutinin ity and the migration inhibitory effect of purified tuberculin protein and herpes x virus type 1 vaccine in patients with recurrent corneal herpes simplex and healthy individuals

	n	T cells (%)	PHA reactivity (cpm/10⁶ lymphocyte)	Migration inhibitory effect of PPD	HSV vaccine
				migration index	
rent herpes phase)	25	67 6 ± 5 7	32309 ± 7571	0 75 ± 0 15	0 95 ± 0 09
rent herpes a 3 months tom free period)	14	68 2 ± 3 5	34055 ± 6354	0 76 ± 0 17	0 80 ± 0 07
hy individuals	17	65 4 ± 6 8	31667 ± 6382	0 76 ± 0 13	0 75 ± 0 13

ificantly lower than in healthy ind iduals ($P < 0\ 01$)

11

Table II
Leucocyte migration inhibitory effect of Herpes *simplex* virus vaccine in patients with recurrent corneal herpes in the active phase of the disease and after a 3 months symptom free period

Patient	Migration index	
	Symptomatic phase	Asymptomatic phase
1	1 04	0 78
2	0 91	0 82
3	0 98	0 77
4	1 03	0 87
5	0 82	0 64
6	1 09	0 91
7	1 02	0 83
8	0 93	0 71
9	0 98	0 80
10	0 90	0 73
11	0 97	0 85
12	0 81	0 83
13	1 03	0 79
14	0 95	0 82
Mean value ± SD	0 96 ± 0 08	0 80 ± 0 07

The difference is significant ($P < 0\ 01$)

There is no explanation of universal validity as to why primary HSV i are subclinical in most individuals yet can be very severe or recurrent in There in no doubt that the recurrent or clinically severe HSV infections occ frequently in neonates and in immunodeficient or immunosuppressed than in healthy adults (Linnemann et al 1973 Muller et al 1973 Nahm 1976) but an immunodeficiency cannot be demonstrated in the majori recurrent herpes patients Virus-specific antibodies can be detected in a s titre in the serum of patients suffering from the recurrent HSV infection (& Allen 1957 Shore et al 1974) When skin testing with HSV an g performed no differences were found in the response of patients with recu ces compared with that of asymptomatic individuals (Russell 1974 Ya 1966)

the first step in the present work in vitro methods were used to study the ral T lymphocyte reaction in healthy individuals and in recurrent corneal es simplex patients The proportions of T lymphocytes in the peripheral blood PHA reactivity and the leucocyte migration inhibitory effect of PPD were the in the two groups This proves that a severe cellular immunodeficiency did xist in the recurrent HSV infection patients Similarly Wilton et al (1972) did find any differences when they compared the lymphocyte responses to PHA and other microbial antigens in seropositive patients without recurrences and tients with clinical exacerbations

the other part of our experiments the cell mediated immunities against the ' antigen were compared In the control group and the recurrent corneal es simplex patients who had been asymptomatic for at least 3 months the HSV ine inhibited the leucocyte migration to almost same extent but it did not cause gration inhibition when the clinical symptoms were manifest Thus indepen ly of whether they suffer from the recurrent HSV infection or not the ntomatic individuals possess cellular immune defence against the virus This iune defence decreased temporarily at the time when the clinical symptoms manifest but is restored after these have subsided On the basis of these lts however it is not possible to decide whether this impairment of the host nce plays a role in the recurrence or whether it represents the immunological equence of this

References

imer H (1971) Lymphocyte transformation test in sympathetic ophthalmitis and the gt Kovanagi Harada syndrome *Brit J Ophthal 55* 850–852

imer H (1974) Cellular hypersensitivity to uveal pigment confirmed by leucoocyte gration tests in sympathetic ophthalmitis and the Vogt Koyanagi Harada syndrome *it J Ophthal 58* 773–776

W H Mendes N F Bianco C & Neussenzweig V (1971) Binding of sheep red blood lls to a large population of human lymphocytes *Nature (Lond) 230* 531–532

ette E H & van Allen A (1957) Laboratory diagnosis of herpetic infections of the eye *Amer J Ophthal 43* 118–126

emann C C May D B Schubert V K Caraway C T & Schiff G M (1973) Fatal viral cephalitis in children with X linked hypogammaglobulinaemia *Amer J Dis Child 126* 0–103

ler S A Herrmann E C & Winkelmann R K (1973) Herpes simplex infections in matologic malignancies *Amer J Med 52* 10?–114

mias A J Alford C & Koronos S (1970) Infection of the newborn with herpes virus ominis *Ad Pediat 17* 18?–2?6

mias A J Visintine A M Caldwell D R & Wilson L A (1976) *Survey Ophth 21* 0–137

Rosenberg G L Synderman R & Notkins A L (1974) Production of chemotactic lymphotoxin by human leukocytes stimulated with herpes simplex virus *Infect* *10* 111–115

Russel A S (1973) Cell mediated immunity to herpes simplex virus in man *Am* *Path 60* 825–830

Russel A S (1974) Cell mediated immunity to herpes simplex virus in man *J Infect* 142–146

Shore S Starr S Wood P & Nahmias A (1974) Detection of cell-dependent antibody to cells infected with herpes simplex virus *Nature (Lond) 251* 350–352

Starr S E Karatela S A Shore S I Duffey A & Nahmias A (1975) Stimulation lymphocytes by herpes simplex virus antigens *Infect Immunity 11* 109–119

Thong Y H Vincent M M Hensen S A Fucillo D A Pleszczynski M & Ball (1975) Depressed specific cell mediated immunity to herpes simplex virus patients with recurrent herpes labialis *Infect Immunity 12* 76–80

Wilton J M A Ivanyi L & Lehner T (1972) cell mediated immunity in herpesvirus infections *Brit Med J 1* 723–726

Yamamoto S (1966) Re-evaluation of the skin test of herpes simplex virus *Jap J* *10* 67–77

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EFFECT OF TRISODIUM PHOSPHONOFORMATE AND IDOXURIDINE ON EXPERIMENTAL HERPES SIMPLEX KERATITIS IN IMMUNIZED AND NON IMMUNIZED RABBITS

BY

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The effect of trisodium phosphonoformate (PFA) has been compared to that of idoxuridine (IDU) when applied topically in both liquid and ointment preparations on herpetic keratitis in rabbits. Trisodium phosphonoformate had a therapeutic effect but was not as effective as idoxuridine in the vehicles tested. This was seen with both herpes-immunized and non immunized rabbits.
A herpesvirus mutant inducing a PFA resistant DNA polymerase was used to infect rabbit corneas. A comparison of the effect of PFA on the keratitis caused by this resistant mutant and the wild type herpesvirus indicates that the therapeutic effect of PFA on the herpes keratitis was due to an inhibition of herpesvirus DNA polymerase.

Key words: phosphonoformate – idoxuridine – herpes keratitis – rabbits – immunized and non immunized – resistant herpesvirus

sodium phosphonoformate (PFA) was recently found to be a selective inhibitor herpesvirus multiplication by inhibiting the viral DNA polymerase (Helgstrand al. 1978, Reno et al. 1978) and to have a therapeutic effect on cutaneous pesvirus infection in guinea pigs (Alenius et al. 1978). Since PFA has a low icity in cell culture (Stenberg & Larsson 1978) and in animals (Flodh et al. 1978) was considered important to compare it to IDU in an experimental herpes atitis model in rabbits.

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Materials

Animals A total of 80 male white rabbits weighing between 2 and 3 kg wer the study All eyes were controlled before each experiment

Viruses and cell cultures Herpes simplex virus type 1 (HSV 1) strain (sensitive to PFA and IDU Strain C 42 VII PFA^r was resistant to PFA as de by plaque assay on AGMK cells (Eriksson & Öberg 1979)

Drugs Trisodium phosphonoformate (PFA) was synthesized according (1924) PFA was used as a 3% aqueous solution in distilled water or as a 3" in water with 0 65% methyl hydroxy propyl cellulose (Methocel® HM neutral pH and as a 5% ointment in a petrolatum base (19% liquid par vaseline 5 PFA) The idoxuridine (IDU) used was commercial preparati IDU solution (Iduridin®) and 0 2% IDU ointment (Iduridin®) As placeb 0 65% Methocel® in saline and petrolatum base were used

Methods

Immunization Rabbits were immunized by injecting 0 1 ml of HSV subcutaneously in both ears Three weeks later the rabbits had a complem titer of 1/8 to 1/32 and were then used for the keratitis experiments

Inoculation One circular epithelial abrasion was made in the central corn animal by touching it with a 5 mm corneal trephine set to a depth of 0 05 eyes were then inoculated with 30 µl of HSV 1 The titer of strain C 42 wa of strain C 42 VII PFA^r 10^7 plaque forming units per ml

Examination and grading All eyes were examined by the same exam performed before and after staining with fluorescein using a slit la examiner did not know which drugs the eyes had received The s epithelial keratitis was graded on a scale of 0 to 3 as follows

Epithelial score *Grade 0* no detectable dendritic ulcer *Grade 0 5* 1 to 4 ulcers limited to the epithelium along the line of abrasion or dendritic limited to the line of abrasion *Grade 1 0* 5 to more dendritic ulcers limi line of abrasion or 2-4 dendritic ulcers not limited to the line of abrasion 5 to 9 dendritic ulcers not limited to the line of abrasion *Grade 2 0* 10-20 ulcers not limited to the line of abrasion *Grade 2 5* more than 20 dendr not limited to the line of abrasion or a confluent ulcer not exceeding on the surface area of the cornea *Grade 3 0* a confluent corneal ulcer invol one third of the corneal surface

istics Standard statistical methods Mann Whitney U test and sign test, were d (Snedecor & Cochran 1969)

atment and experimental design In non immunized animals PFA was applied ically in one eye and IDU in the other eye of each animal. Placebo-treated trol eyes were treated with either saline 0 65% Methocel® or petrolatum base solutions were given as one drop per eye Ointment (0 1 ml) was applied with a nge in the lower fornix of each eye Treatment started on day 2 post virus culation and continued for 4 days Treatment of immunized rabbits started at 3 and continued for 4 days The effect of 5% PFA ointment on the keratitis sed by strain C 42 was compared to the effect on the keratitis caused by strain C VII PFA One eye was treated with the 5% PFA ointment and compared to cebo treatment of the other eye on the same animal The PFA treated eye was red as better if the epithelial lesion grade was at least 0 5 lower than the control worse if it had at least a grade of 0 5 higher and same if the grades were the ne Treatment started on day 3 post virus inoculation and continued for 4 days PFA and IDU were also applied to non inoculated eyes to test for toxicity

Results

ct of PFA in different vehicles

e reduction in keratitis score after treatment with 3% PFA in water and 0 1% U solution is shown in Fig 1 IDU caused a rapid decrease in score but at days 6 nd 10 an increase in keratitis score was seen IDU had a significantly better effect n PFA on the keratitis score at day 4 ($P<0\ 01$) 6 ($P<0\ 01$) and 8 ($P<0\ 05$)

To increase the ocular bioavailability of PFA a solution of 3% PFA in 0 65% thocel® was used and compared to 0 1% IDU solution As shown in Fig 2 PFA luced the keratitis score on day 4 ($P<0\ 01$) and 6 ($P<0\ 01$) when compared to cebo IDU reduced the keratitis scores more than PFA on day 4 ($P<0\ 05$) but not any other day Even in this experiment an increase in the keratitis score was served in the IDU treated eyes at days 6 and 10 after inoculation

The results were similar when the effect of a 5% suspension of PFA in a trolatum base was compared to a 0 2% IDU ointment Treatment with IDU ntment resulted in a lower keratitis score at days 4 and 8 than that seen with PFA ntment

No toxic effects from PFA or IDU that is punctate keratopathy increasing iritis conjunctivitis were noted in the vehicles tested

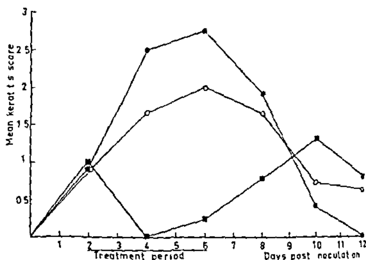


Fig 1

Comparison of PFA water solution and IDU solution in treatment of herpes kera Treatment started 2 days post inoculation all treatments were given every hour durng day (12 h) and every second h during the night (12 h) for 4 days ■——■ 19 eyes w treated with 0 2% IDU solution O——O 12 eyes were treated with 3% PFA water solu ●——● 6 eyes were placebo treated with saline

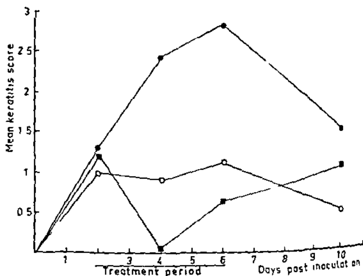


Fig 2

Comparison of PFA as a Methocel® solution and IDU solution in treatment of herpes ker Treatment started 2 days post inoculation all treatments were given every second h for 4 ■——■ 7 eyes were treated with 0 2% IDU solution O——O 7 eyes were trea ed with PFA Methocel solution ●——● 7 eyes were placebo treated with 0 65% Methocel

eatment of herpes keratitis in immunized rabbits

oculation of HSV 1 C 42 in rabbits immunized with the same strain of virus sulted in an infection with less conjunctivitis and injection than in non immunized imals and without iritis In these animals the epithelial keratitis developed thout total destruction of the cornea which is sometimes observed in non munized rabbits The effects of treatment with PFA and IDU were similar to that n in non immunized rabbits

eatment of herpes keratitis caused by a PFA resistant virus

e mechanism of the therapeutic effect of PEA was investigated by the use of a rpersvirus mutant resistant to PFA Table I shows a comparison of the effect on rpes keratitis caused by a sensitive (C 42) and a resistant (C 42 VII PFA) strain of rpesvirus Each animal was inoculated with the same type of virus in both eyes d the severity of the keratitis was compared within each animal The average verity of the keratitis caused by the sensitive and the PFA resistant virus was similar day 3 post inoculation Treatment with PFA had a better ($P<0\ 01$) therapeutic fect on the keratitis caused by the sensitive virus than by the resistant virus

Table I
Effect of PFA on keratitis caused by sensitive and resistant HSV 1

Days post inoculation	C 42 Condition			C 42 VII PFA Condition		
	B	S	W	B	S	W
3	0	7	1	0	6	2
4	6	2	0	3	4	1
6	7	1	0	4	4	0
8	6	2	0	3	2	3

Treatment started 3 days post inoculation all treatments were given 5 times daily for 4 days Eight animals were used for the sensitive (C 42) and eight for the resistant (C42 VII PFA^r) HSV 1 strain. The figures show the number of eyes judged as better (B) same (S) or worse (W) when compared to the placebo treated eyes as described in Methods

Discussion

The therapeutic activity of anti herpesvirus drugs given topically in the eye depend both on the antiviral activity per se and on the concentration reached in corneal cells

It is likely that after topical application the intracellular concentration of nucleoside analogs (like IDU) which are phosphorylated and trapped in corneal cells will be higher than that of PFA which is not metabolised and probably easily can leave the cell (Flodh et al 1978 Stenberg & Larsson 1978) Even the Methocel® enhanced the activity of PFA IDU still showed a slightly therapeutic activity although late during infection a rebound was observed in IDU treated eyes

As pointed out by Markham et al (1977) it should be of antiviral effects of different compounds in an animal model with a immune response to herpes simplex virus as this would be closer to the human keratitis The effect of treatment with IDU and PFA did not differ between immunized and non immunized rabbits

The PFA resistant herpesvirus mutant used induces a DNA polymerase which resistant to PFA (Eriksson & Öberg 1979) The lack of therapeutic activity of PFA on a herpes keratitis caused by this resistant mutant (Table I) indicates mechanism of action of PFA on herpes keratitis is an inhibition of the viral DNA polymerase

PFA did not have a better therapeutic activity than IDU in our experiments might yet be of clinical interest The cellular toxicity of PFA has been shown to lower than that of IDU or ara A (Helgstrand et al 1978) Furthermore mechanism of action by PFA differs from that of IDU and IDU resistant sensitive to PFA (unpublished observation)

References

Alenius S Dinter Z & Öberg B (1978) Therapeutic effect of trisodium phosphonoformate on cutaneous herpesvirus infection in guinea pigs Antimicrob Agents Chemother 408–413

Alenius S & Öberg B (1978) Comparison of the therapeutic effects of five antiviral agents on cutaneous herpesvirus infection in guinea pigs Arch Virol 58 277–288

Eriksson B & Öberg B (1979) Characteristics of herpesvirus mutants resistant to phosphonoformate and phosphonoacetate Antimicrob Agents Chemother 15 758–762

Flodh H Helgstrand E Lundstrøm J & Öberg B (1978) Antiviral pharmacokinetics and toxic properties of phosphonoformic acid 18th Interscience Conference on Antimicrobial Agents and Chemotherapy AMS Abstract 212

gstrand E Eriksson B Johansson N G Lannero B Larsson A Misiorny A Noren J Sjoberg B Stenberg K Stening G Stridh S Öberg B Alenius S & Philipson L. 979) Trisodium phosphonoformate a new antiviral compound *Science 201* 819–821

-kham R H C Carter C Scobie M A Metcalf C & Easty D L. (1977) Double blind clinical trial of adenine arabinoside and idoxuridine in herpetic corneal ulcers *Trans ophthal Soc U K* 97 333–340

en P (1924) Beitrag zur Kenntnis der organischen Phosphor Verbindungen *Chem Ber* 7 1023–1038

o J M Lee L. F & Boezi J A (1978) Inhibition of herpesvirus replication and herpesvirus induced deoxyribonucleic acid polymerase by phosphonoformate *Antimicrob Agents Chemother 13* 188–192

decor G W & Cochran W G (1969) Statistical Methods 6th ed The Iowa State niversity Press Ames

berg K & Larsson A (1978) Reversible effects on cellular metabolism and proliferation y trisodium phosphonoformate Antimicrob *Agents Chemother 14* 727–730

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ASTIGMATISM AND SURFACE PHENOMENA IN PTERYGIUM

BY

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Examination of 39 eyes with pterygium and 17 contralateral eyes revealed increased astigmatism with the rule (> 0 5 D in 46% ≧ 4 D in 13%) without associated impairment of vision
Intensified vital staining was seen to be provoked over the pterygium by tetrazolium and rose bengal whereas this was not the case with fluorescein or alcian blue There were no signs of desiccation (Break up time normal)
Stocker s line in front of the pterygium was observed in 46% In 13% this was continuous with Hudson Stähli s line
A quantitative cytologic study disclosed keratinisation in 5% Increased desquamation was seen in 10 %
The central thickness of the cornea was the same as in normal eyes

Key words pterygium – astigmatism direct – BUT – vital staining – Stocker s line – cytology quantitative

The pathogenesis of pterygium is in the main obscure Ultraviolet light (Came 1965 Forsius et al 1963 Hogan et al 1967) and perhaps also dryness of the co are suspected as possible provoking factors The prognosis is unknown Ex towards the centre and development of astigmatism are phenomena to be fe

Some workers have noticed astigmatism with the rule and others against the (Forsius et al 1962 Bedrossian 1960)

For further elucidation of these matters we decided to summon pter patients to be examined for astigmatism and surface phenomena and dryness

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Material

ygium is a rare defect within our territory, i.e. Greater Copenhagen (Norn 9). We summoned patients from the files collected over a period of several years ur hospital and also from ophthalmic practice.

he series examined comprised 30 patients of whom two were found to have idopterygium and accordingly had to be ruled out. (A probe could be passed npeded from the upper to the lower edge along the limbus under the lge formed mucosal fold.)

Thus 28 patients were left with a proper pterygium. Of these 11 had pterygium oth eyes and 17 of one eye. In other words there were 39 eyes with pterygium 17 control eyes without this defect.

ne were females and 23 males. Only 15 were Danes while 13 were foreign ourers, the majority Turks and Pakistanis.

Their ages ranged from 20 to 85, mean age 52 years.

Methods

gmatism was measured using Javal's keratometer. Values above 0.5 D were characterized as gmatism.

e break up time (BUT) was measured initially as described by Norn (1974). Values below 10 onds represented pathological dryness.

al staining was performed using first a rose bengal fluorescein mixture, and some hours r a tetrazolium alcian blue mixture as described by Norn (1974).

The numbers of stained dots in the individual regions were graded from 1 to 5 responding to <30, <100, <1000, <10 000, and >10 000 dots.

ologic examinations were based on scrapings from the pterygium and quantitative pipette nples from the inferior fornix of pterygium affected eyes and control eyes.

Table I

Dimensions of pterygium. Range ( )

		Pterygium N = 39	Unilateral pterygium N = 17
Breadth	(mm)	2.42 (0.2–5.0)	2.47 (1.0–5.0)
Height	(mm)	4.39 (1.0–7.0)	4.29 (2.0–6.5)
Area	(mm^2)	5.78 (0.2–16.25)	5.55 (1.0–16.25)

Presence of more than 50 keratinized nuclear squamous cells in the pipette indicated keratinisation and presence of more than 50 columnar epithelial cells desquamation (for details vide Norn 1974)

The *central corneal thickness* was measured by means of the Haag Streit attachment I. The width area was excluded from the measurement by bringing the double line of the corneal surface to a level line with the corresponding line of the endothelial surface method A Norn 1974) Another method employed (method B) was that of measuring using the thinnest possible optical section presumably including the precorneal film.

Result

Site All 39 pterygia were localized nasally never temporally

Dimensions are shown in Table I In one case the pterygium measured 5 0 horizontally from the limbus and in one case 4 0 mm In the remaining under 4 0 mm No difference was seen between unilateral and bilateral cases material comprised both small and rather large pterygia

Astigmatism was in most cases with the rule both in the pterygium affected eyes in the control eyes with a radius of curvature exceeding 7 5 mm (Table II)

We rarely saw astigmatism against the rule (inverse indirect senile') or oblique astigmatism

The *degree of astigmatism* averaged 1 44 dioptres (D) for the 39 pterygium against 0 77 D for the control eyes The difference is not significant. The highest degree of astigmatism seen was 4 5 D (one pterygium case) 4 D was observed in

Table II
Astigmatism (> 0 5 D) in % in pterygium affected eye and contralateral eye

	Pterygium N = 39	Unilateral pterygium N = 17	Control eye N = 17
Astigmatism direct	46	59	47
Astigmatism indirect	10	0	6
Astigmatism oblique	8	6	6
direct ≧ 2 D	18	24	0
direct ≧ 4 D	13	12	0
vision ≦ 6/9	18	12	18

Table III
Surface phenomena in pterygium in %

	Pterygium N = 39	Unilateral pterygium N = 17	Control eye N = 17
Stocker s line	46	41	–
Hudson Stahli s line	33	29	18
BUT over pterygium <10 seconds	21	29	–
BUT whole cornea <10 seconds	5	12	6

gium affected eyes Among the control eyes maximum was 1 75 D At ontal pterygium dimensions of 3 mm or more the astigmatism averaged 1 97 ainst 1 11 D in eyes with smaller pterygia This tendency is not significant r (Mann Whitney s rank sum test and Student s *t* test)

visual acuity was impaired even with optimum correction owing to cataract tes or senile changes but hardly in any case to pterygium induced astigmatism ontrol eye in Table II)

ers line is a punctate brownish subepithelial line passing vertically in front of nvasive apex of the pterygium It was present in about half of the cases (Table with no relation to the type of astigmatism the size of the pterygium vital ability or BUT

on Stahli s line is a line passing horizontally below the corneal centre The line seen to have curve shaped contact with Stocker s line in five of the 18 cases in h the latter occurred i e in 13% (5/39) of all the eyes with pterygium

ie frequency of occurrence of Stahli s line was not significantly higher among pterygium affected eyes than among the control eyes

break up time (BUT) averaged 36 8 seconds in the pterygium affected eyes and seconds in the control eyes BUT was 42 0 seconds in front of the apex of the ygium (The figures are minimum figures the test having been discontinued 60 *seconds in 18%* of the cases) In no more than two cases was the *BUT* value over the apex of the pterygium both without Dellen formation BUT was wise zero in one control eye

bengal vital staining was significantly more frequent on the surface of the ygium than on the cornea (Table IV $P < 0.01$) No particularly intense staining noticed in front of the base of the pterygium

Table IV
Vital staining of pterygium remaining cornea and contralateral eye in %

	Pterygium N = 39	Cornea of pterygium affected eye N = 39	Cornea of control eye N = 1[illegible]
Rose bengal	54	13	24
Fluorescein	64	46	41
Tetrazolium	59	18	12
Alcian blue	18	8	0

Alcian blue rarely stained the pterygium no more than the cornea

Fluorescein vital stained pterygium and cornea to equal extents Staining grad[illegible] on the pterygium and 0 79 on the cornea (control eye 0 76)

Tetrazolium stained the pterygium more frequently (Table IV $P < 0.01$) and intensely (grade 0 97) than the cornea (grade 0 23 control eye 0 [illegible]4) Of the pterygia 10 were stained by tetrazolium alone 8 by rose bengal alone and both dyes

The *central corneal thickness* was normal in the pterygium affected eye com[illegible] with the control eye A systematic difference was noted between the two pach[illegible] methods employed method B having given an about 20 µm greater thicknes[illegible] method A

Cytology

Cytologic examination most often gave the same results as in normal eyes

Keratinisation was disclosed in two and increased desquamation in four of [illegible] quantitative pipette samples One showed signs of bacterial conjunctivitis (ow[illegible] neutrophilic granulocytes) while virus infection was suspected in three (ow[illegible] lymphocytes)

Scrapings from the pterygium showed eight out of 39 to be suspe[illegible] keratinisation (more than 10% nuclear squamous cells had vacuoles or k[illegible] granules)

No correlation was demonstrated between the size of the pterygi[illegible] stainability and pathological cytology

Table 1
Central thickness of cornea of pterygium affected eyes (N = 39) compared with control eyes (N = 17)
Pachymetric methods A and B vide text

	Method	Cornea thickness (mm)	SEM
Pterygium affected eyes	A	0 483	± 0 007
Pterygium affected eyes	B	0 504	± 0 007
Control eyes	A	0 488	± 0 011
Control eyes	B	0 506	± 0 009

Discussion

ıus & Eriksson (1962) found inverse astigmatism to be the most frequent type ng their 47 eyes with small pterygia The inverse astigmatism may however be idered as a senile phenomenon

ı the present series of 39 pterygia of different sizes astigmatism with the rule lominated being often of a very pronounced degree Note however that the rence from the control eyes was not significant presumably because the rol series was numerically small (17 eyes)

he results of the present study bear out the view that a pterygium presses nst and flattens the cornea thus increasing the horizontal radius of curvature visual acuity remains unaffected provided the patient is supplied with suitable ses

Ve have never seen a pterygium extend as far as the centre of the eye neither in enland nor in Copenhagen (Norn 1979 an additional number of 79 pterygia) the pterygia of our total series were localized nasally Exceptions from this rule he literature may be due to pseudopterygia

tocker (1939) believed that the line discribed by him in front of the base of the rygium is due to a bend of the cornea at right angles to the flattest corneal ridian He based his view on two cases observed of which No 2 presumably was of pseudopterygium being located infero-temporally on the cornea The ervations made in the series under review do not bear out the theory of a bend ıcker s line was seen to be continuous with the horizontal Hudson Stahli s line tahli s line is present in many normal eyes (Norn 1968)

uperficial depositings presumably of iron are responsible for the occurrence of se two lines Their sites are probably accountable for by thickened layers of tears ıhli s line corresponding with lacrimal river between the lower lid margin and the

cornea and Stocker s line representing the corresponding layer of tears be the projecting base of the pterygium and the cornea

Barraquer (1965) Mackie (1971) and Paton (1935) hold that dryness o base of the pterygium causes the latter to grow in size

Goldberg (1976) on examination of 59 pterygia by Schirmer s test and I found no evidence to support this view

Neither did the present study reveal signs of dryness The pterygium itsel certainly often stained by rose bengal but tetrazolium disclosed a similar d epithelium above the pterygium

Staining by tetrazolium is no indication of dryness (reveals reducing enz epithelial cytoplasm) The stainability must be interpreted as an action o surface epithelium of the pterygium whereas not as the cause of growth of pterygium

Fluorescein staining was surprisingly frequent This was accountable for strain caused by the examination prior to vital staining (eye forced to remain for a long time during examination for BUT etc)

References

Barraquer J I (1965) La discontinuite localisee du film lacrymal precorneen *Ophth* *150* 111–122

Bedrossian R H (1960) The effects of pterygium surgery on refraction and co curvature *Arch Ophthal (Chicago) 64* 553–557

Cameron M F (1965) Pterygium througout the world Charles C Thomas Springfield

Forsius H & Eriksson A (1962) Pterygium and its relation to arcus senilis pingue other similar conditions *Acta Ophthal (Kbh) 40* 402–410

Forsius H & Eriksson A (1963) Die Frequenz von Pingvecula und pterygium bei La Aussenarbeitern *Klin Monatsbl 142* 1021–1030

Goldberg L & David R (1976) Pterygium and its relationship to the dry eye in the Bant *J Ophthal 60* 720–721

Hogan M J & Alvarado J (1967) Pterygium and pingvecula Electronmicroscopi *Arch Ophthal (Chicago) 78* 174

Mackie I A (1971) Localized corneal drying in association with Dellen pterygia and r lesions *Trans Ophthal Soc U K 91* 129–145

Norn M S (1968) Hudson Stahlis line of cornea *Acta Ophthal (Kbh) 46* 119–199

Norn M S (1974) External eye Methods of examination p 200 Scriptor Copenhagen

Norn M S (1979) Prævalensen af pterygium oculi pa Grønland og i København *Ugeskr* *141* 214–216

D (1975) Pterygium management based upon a theory of pathogenesis *Trans amer d Ophthal Otolaryng* 79 603–612
r F (1939) Eine pigmentierte Hornhautlinie beim Pterygium *Klin Monatsbl Augenheilk* 384–388

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TEAR FLOW AND SOFT CONTACT LENSES

BY

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Tear flow was determined in 14 persons before and after one month of adaptation to a soft contact lens (Soflens® Bausch & Lomb) by means of a radioactive tracer (technetium Tc^{99m} as pertechnetate) a gamma camera and a computer system The elimination of the radioisotope from the conjunctival sac was diphasic with a significant increase of the fractional turnover rate after the adaptation period in the initial phase with a rapid elimination, but no change in the basal phase with a slower elimination The fractional turnover rate was also determined with the soft contact lens placed on the cornea after having been pre soaked in the technetium solution resulting in a value of 0 0?? $\pm$ 0 003 min^{-1} (mean $\pm$ SEM n = 12) The fractional turnover rate resulting from instillation of the radioisotope on the non pre soaked soft contact lens placed in the eye was found to 0 020 $\pm$ 0 004 min^{-1} (mean $\pm$ SEM n = 6) In the studies with the soft contact lens in the eye the elimination curves were monophasic and not diphasic as in normal tear flow studies

Key words tear flow – technetium – gamma camera – soft contact lenses – human

In fitting guides for soft contact lenses it is often reckoned that tear deficiencies are a relative contraindication for contact lens wear On the other hand authors have reported the results of treatment of dry eyes with soft contact lenses

A stimulation to the normal human eye will result in an increased tear flow ... few min In the adaptation period to a contact lens the patients often experience watery eyes for some time The gradual return to normal conditions could be explained by a fatigue block as described by Jones (1966) In patients f... hard contact lenses the decrease in corneal sensitivity could be responsible f...

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alization of lacrimation in the adaptation period whereas this can not be the nation with soft contact lenses causing almost no changes in corneal sensitivity odot 1974 1976)

e purpose of this paper was to study the possible effect of a well adapted soft ct lens on tear flow determined by means of a radioactive tracer and a dynamic na camera detection system with and without the soft contact lens placed on uman eye

Material

material comprised 18 human volunteers – 4 males and 14 females – in the age p 20 to 30 years They were fitted with Soflens® (Bausch & Lomb) according to manufacturer s fitting schedule All the volunteers were myopic (range –1 50 2.5 dioptres) except one with a low grade of hypermetropia The patients were ked by slit lamp microscopy ophthalmoscopy and keratometry Vital staining Rose Bengal and fluorescein was carried out to exclude persons with corneal ormalities Tear break up time was found normal (over 20 seconds) Most of the nteers joined the group of persons comprising the material of normal persons tear flow study (Sørensen & Taagehøj Jensen 1979) Four of the patients only d the fourth determination

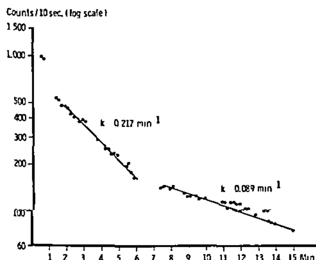


Fig 1

r flow curve from a normal person without contact lenses with an initial phase from 2-6 min and a basal phase from 7 5 15 min after instillation

Method

The method has been described in detail in another paper (Sørensen & Ta Jensen 1977 1979) The parameter for tear flow the fractional turn calculated from the elimination curves of the radioisotope (technetium T pertechnetate) from the conjunctival sac The patients were placed in position with the head fixed under the pinhole collimator in the volume of 10 µl of a normal saline solution with the technetium was instilled center of the cornea (dose 100 200 µCi) The fractional turnover rate (Fig calculated in the initial phase (approximately 2 5 min after instillation basel phase (7 5 15 min after instillation) Four determinations were carried the same eye 2 before the fitting of the soft contact lens and one a adaptation period of at least 3 weeks This third determination was without a soft lens on the eye immediately after removal of the lens but wi lens on the fellow eye In the fourth measurement the contact lens was pl eye during the recordings In 12 of these determinations with the soft len eye the lens was pre soaked in a 10 fold diluted technetium solution for before the recordings whereas 6 of the studies were carried out by instillation undiluted radioisotope solution on the soft contact lens placed on the cornea

All tear flow determinations were corrected for background radiation a in a previous paper (Sørensen & Taagehøj Jensen 1979)

Results

The second determination before adaptation was compared to the deter after adaptation (in 2 cases the first determination was used because the determination failed) As shown in Table I the mean fractional turnover ra initial phase was found to be higher after adaptation (t test for paired dat 2P 5 5%) whereas the basal fractional turnover rate was of the same magnitu adaptation (t test for paired data $2P = 20$ 30%) The elimination curves and after adaptation were all diphasic in a semilogarithmic plot

When a pre soaked soft contact lens was placed on the eye the radioactiv be seen accumulated corresponding to the position of the soft lens on the (Fig 2) with some radioactivity entering the lacrimal pathway A similar r was seen when a non pre soaked lens was placed on the cornea followed instillation of 10 µl technetium solution directly on the soft contact le s Re small amounts of radioactivity was seen in the conjunctival sac outside the in both cases

Table I

Fract onal turno er rate before and af er adapta on to a sof contact lens and fract onal turno er ra es rep esent ng the el m na on of technet um from soft lenses (mean ± SE)

	In tial	Ba al
Before adapta on (second determ nat on (n 14)	0 173 + 0 015 (m n⁻)	0 076 + 0 006 (m n)
Af er adap at on (h rd determ nation (n 14)	0 204 + 0 014 (m n⁻¹)	0 069 + 0 006 (m n⁻¹)
Sof contact lens pre soaked n d lu ed technet um solution (n 12)	0 021 + 0 003 (m n)	
Sof contact lens pla ed on the cornea during nst llation of technet um (n = 06)	0 0 0 + 0 004 (m n⁻¹)	

W th the soft lens placed on the cornea whether pre soaked or not pre soaked el m nation curves turned out to monophas c n the s milogarithm c plot (Fig The fract onal turno er rate was 3-4 times smaller than in the basal phases n r flow stud es w thout a contact lens in the eye The d fference between the e soaked and non pre soaked group was not statistically s gn f cant

D scussion

pers stent irritation to the conjunctiva has been said to provoke a fatigue block which is thought to be a block in the efferent nerves to conjunctival sensory impulses (Jones 1966) Whether a fatigue block can be caused by a contact lens seems not to be known though the assumption is ob ious

Th s study showed that the tear flow was not decreased by the adaptat on to a soft ntact lens Thus a reduced tear secretion cannot be regarded as a cofactor in the elopment of depos ts on soft contact lenses in normal persons On the contrary a ndency to a small increase in the in tial tear flow was found

The el m nation curves with the soft contact lens placed on the cornea were onophasic with an el minat on of approximately 27 /m n Th s slow monophas c

Fig 2

The distribution of technetium in an eye fitted with a soft contact lens The radioac accumulated in the lens Radioactivity is also seen in the lacrimal pathways Three scint with different degree of exposure are shown Some radioactivity has entered th

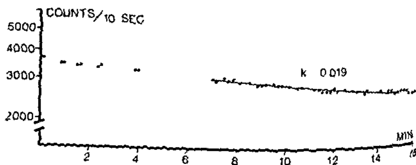


Fig 3

Elimination of technetium from a soft contact lens on a human eye Radioactivity in the conjunctival sac area including the soft lens plotted versus time in a semilogarithmic m Each dot represents a recording in a ten second interval

ination was not a result of a fatigue block because the elimination curves in persons wearing hard lenses have a diphasic shape like the curves in normal persons without contact lenses (personal observation to be published later). The explanation may be that the negatively loaded pertechnetate was accumulated in the soft contact lens and that the elimination curves represented the elimination of the radioisotope from the contact lens material. The monophasic shape suggested that the elimination curve was dominated by the elimination from the lens making the elimination from the conjunctival sac invisible.

In the pre soaked and non pre-soaked lenses were found fractional turnover rates of the same magnitude. This means that the technetium after uptake by the lens has been bound in the lens material in a way resulting in an elimination of %/min when the lens was placed on a human eye.

These results add to the interest of the soft contact lens-drug relationship. It seems obvious that some drugs will be retained in the lens material in the similar way as technetium with prolonged corneal contact times. However the elimination of most drugs from soft materials during in vivo conditions is unknown and probably depends on the chemical binding between the drug and the lens material.

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References

Jones L. T. (1966) The lacrimal secretory system and its treatment. *Amer. J. Ophthal.* 62: 47–60.

Millodot M. (1974) Effect of soft lenses on corneal sensitivity. *Acta ophthal. (Kbh.)* 52: 603–608.

Millodot M. (1976) Effect of the lenght of wear of contact lenses on corneal sensitivity. *Acta ophthal. (Kbh.)* 54: 721–730.

Sørensen T. & Jensen F. T. (1977) Methodological aspects of tear flow determination by means of a radioactive tracer. *Acta ophthal. (Kbh.)* 55: 726–738.

Sørensen T. & Jensen F. T. (1979) Tear flow in normal human eyes. Determination by means of radioisotope and gamma camera. *Acta ophthal. (Kbh.)* 57: 564–581.

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THE HLA SYSTEM IN PRIMARY OPEN ANGLE GLAUCOMA AND IN PATIENTS WITH PSEUDOEXFOLIATION OF THE LENS CAPSULE (EXFOLIATION OR FIBRILLOPATHIA EPITHELIOCAPSULAR

BY

J E SLAGSVOLD and R NORDHAGEN

HLA typ ng of e ghteen ant gens in 43 pat ents w h pseudoexfolia n of the lens capsule 45 pat ents w th capsular glaucoma and 43 pat ents w h primary open angle glaucoma was performed No s gn f cant dev at on f om a control series of 45 subjects was found

Key w rd pseudoexfoliat on glaucoma – ant gens HLA

Many associations between HLA and disease have been reported especial diseases where an immunological mechanism is suggested (Ryder & S eg 1976) In ophthalmology the association between HI A B27 and acut an uveitis is well known (Brewerton et al 1973) and used as a diagnostic crite HLA compability is considered important for the o itcome of corneal gr (Ehlers 1977)

Becker et al (1962) suggested that immune mechan sm m ght be of impor in primary open angle glaucoma HLA typing of these p t ents showed an exc HLA B7 and HLA B12 (Sh n & Becker 1976) Increased prevalence of HLA in primary open angle glaucoma was reported by Waltman et al (197 O have failed to confirm these observations (Grumet et al 1971 Henley et al Aviner et al 1976 Grabner & Mayr 1977 Brown et al 1978 Damgaard Je Kissmeyer Nielsen 1978)

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Scandinavia many studies of pseudoexfoliation and capsular glaucoma have reported discussing sources of the pathological substance and the relationship een pseudoexfoliation capsular glaucoma and primary open angle glaucoma de 1956 Tarkkanen 1962 Bertelsen et al 1964 Hansen & Sellevold 1968)

far as we know HLA typing has not been performed in these patients iously The purpose of this study was to see if HLA typing could give additional mation of the relationship between the different groups and may be explain onflicting reports of HLA types in primary open angle glaucoma

Materials and Methods

v three patients with pseudoexfoliation and normal intraocular pressure (< 19 Hg) and normal optic discs forty three patients with primary open angle coma and forty five patients with capsular glaucoma (intraocular pressure > 21 Hg pathological disc cupping and characteristic visual field defects) were

Table I

Frequencies of A–locus and B locus Antigen Specifities

HLA ntigen	PE N=43	CG N 45	POAG N 43	Controls N=45	χ^2	P_{corr}
A_1	11	19	19	11	2 99	
A_2	27	25	23	27		
A_3	9	11	15*	7	3 41	
A_9	15	8	5	10	1 67	
A_{10}	4	1	2	5		
A_{11}	5	7	6	1		
A_{28}	1	3	–			
B_5	–	2	–	3		
B_7	14	6	18	9	3 97	0 90
B_8	9	19*	15	11	2 45	
B_{12}	11	18*	7	7	5 54	0 36
B_{13}	–	–		1		
B_{14}	1	–	2	1		
B_{15}	15	8	7	13		
B_{17}	–	2	2	3		
B_{27}	6	6	3	4		
Bw_{35}	4	6	3	6		
B_{40}	9	11	8	9		

test compared to controls

Pseudoexfoliation CG capsular glaucoma POAG primary open angle glaucoma

chosen randomly Forty five individuals not belonging to any of these grou with minor eye complaints served as controls Both the patients with primar angle glaucoma and the controls were examined in mydriasis to exclude pse foliation material Pseudoexfoliation represents an old age phenomenon, patients and controls attending the study had passed 55 years (mean /3 1? mean age in each group was Pseudoexfoliation 71 62 capsular glaucoma primary open angle glaucoma 73 51 controls 73 31

The sex distribution was (F/M) Pseudoexfoliation 33/10 capsular gl 28/17 primary open angle glaucoma 26/17 controls 26/19

All subjects were from a relatively homogenous population living within of the hospital

HLA typing of 18 antigens with 55 antisera was performed using recomm microcytotoxicity techniques All patients and controls were typed blind the laboratory knowing the diagnosis Two-by two chi square test with correction was used for statistical analyses Corrected *P* value (P_{corr}) was f multiplying the *P* value with the number of antigens tested for i e 18 (Grur al 1971)

Results

The distribution of the HL A and B antigens in the different groups is sh Table I

The antigen frequencies in the pseudoexfoliation capsular glaucoma and ry open angle glaucoma groups did not differ significantly from the control B12 seems to be increased in patients with capsular glaucoma $\chi^2 = 5\ 54$ *P* however $P_{corr} < 0\ 36$ Likewise there seems to be an increased frequency o B7 in primary open angle glaucoma but again this is not significant (χ^2 $P_{corr} < 0\ 90$)

Discussion

In this study we have not been able to demonstrate an association betwee antigens and primary open angle glaucoma capsular glaucoma or pseudo tion

The different results of various investigations of HLA typing in priman angle glaucoma have been discussed by Damgaard Jensen & Kissmeyer (1978) and Brown et al (1978) taking racial ethnic socioeconomical age & diagnostic criteria differences into consideration

The control population of Shin et al (1977) was racially mixed No atte

ı made to match patients and controls (Damgaard Jensen & Kissmeyer Nielsen -8) Futhermore it is not mentioned whether pseudoexfoliation was looked for -driasis) in primary open angle glaucoma in any of the studies

ur patients and controls were selected in order to get comparable groups ding the above mentioned difficulties although this involved that smaller ıps of patients were investigated (materials) However even if we found an eased prevalence of HLA B12 in capsular glaucoma patients and of HLA B7 rimary open angle glaucoma patients P_{corr} values showed that the differences insignificant at the 5% level Shin et al (1977) did not multiply their P values by number of antigens examined This would make the increased prevalence of A B7 insignificant Still it is interesting that a trend towards an increased uency of HLA B7 and B12 was also demonstrated in our material and the rse relationship of these antigens in patients with capsular glaucoma and nary open angle glaucoma might call for futher investigation Such a study uld preferably include typing for HLA D antigens since associations to disease ten more clearly demonstrated with these antigens

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References

ıer A Henley W I Fotino M & Leopold I H (1976) Histocompatibility (HLA) antigens nd primary open angle glaucoma *Tissue Antigens* 7 193–200

ker B Keates E U & Coleman S L (1962) Gammaglobulin in the trabecular meshwork f glaucomatous eyes *Arch Ophthal (Chicago) 68* 643–647

ielsen T I Drabløs P A & Flood P R (1964) The so-called senile exfoliation seudoexfoliation) of the anterior lens capsule a product of the lens epithelium ibrillopathia epitheliocapsularis A microscopic histochemic and electron microscopic ıvestigation *Acta ophthal (Kbh) 42* 1096–1113

werton D A Caffrey M Nichols A Walters D & James D C O (1973) *Lancet 2* 94–996

wn R H Lichter P R & Haines R F (1978) The HLA system and primary open angle laucoma *Tissue Antigens 12* 151–159

ngaard Jensen I & Kissmeyer Nielsen F (1978) HLA histocompatibility antigens in pen angle glaucoma *Acta ophthal (Kbh) 56* 384–388

ers N (197.) Corneatransplantasjon *Tidsskr Nor Lægefor 139* 2673–2678

ibner G & Mayr W R (1977) Histokompatibilitatsant gene (HLA ant gene) und Offen inkel-Glaukom *Albr v Graefes Arch 202* 75–79

Crumet F C Coukell A Bodmer J G Bodmer W F & McDevitt H
Histocompatibility (HLA) antigens associated with systemic lupus erythematosus
J Med 285 193–196

Hansen E & Sellevold O J (1968) Pseudoexfoliation of the lens capsule
evaluation with special regard to the presence of glaucoma *Acta ophthal*
1095–1104

Henley W L Leopold I H & Avner Z (1974) *Lancet 2* 1973

Ryder L P & Svejgaard A (1976) *Associations between HLA and disease* Report fro
and disease registry of Copenhagen Compactas Copenhagen

Shin D H & Becker B (1976) The prognostic value of HLA B12 and HLA B7
patients with increased intraocular pressure *Amer J Ophthal 82* 871–874

Shin D H Becker B Waltman S R Palmberg P F & Bell C E (1977) The pr
HLA B12 and HLA B7 antigens in open angle glaucoma *Arch Ophthal (C*
224–225

Sunde O A (1956) On the so-called senile exfoliation of the anterior lens capsul
and anatomical study *Acta ophthal (Kbh)* Suppl 45

Tarkkanen A (1962) Pseudoexfoliation of the lens capsule *Acta ophthal (Kbh)* Sup

Waltman S R Palmberg P Newton W & Becker B (1975) Glaucoma and HL
Lancet 2 927

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ULTRASONOGRAPHIC STUDY OF DIABETIC VITREO RETINAL DISEASE WITH LOW VISUAL ACUITY

BY

BENGT JERNELD PEEP ALGVERE and GUR SINGH

N nety three d abetics (168 eyes) w th opaque ocular med a and low visual acu ty (range amauros s to 0 1) were exam ned by ultrasonography (A and B scan) us ng a Coleman Ophthalmoscan 100 Dense vitreous membranes were found n 112 (67%) eyes 100 (60%) of wh ch showed posterior membra nes Preret nal or prepap llary prol ferat ons (extraret nal stalks) were demon strated n 71 (49%) eyes Fifty four (32%) eyes had ret nal detachments (40 local zed 14 total) These were present in 10 (50%) of the 20 amaurotic eyes The ultrason c accuracy was checked n 49 eyes at v trectomy It was 78% for retinal detachments and 67% for prepap llary and preret nal proliferat ons The stalks circumscribed with n 2 mm or less were the hardest to detect Ultrasonography thus a ds to pred ct the prognos s after vitrectomy The visual prognosis appears to be much more opt mistic in eyes w th v treous membranes and prepap llary proliferations than in those with vitreous mem branes associated with preretinal prol ferat ons

Key words ultrasonography B scan d abetes vitreo-retinal disease — v trectomy

liabetes mell tus the retinal microangiopathy in itself can cause loss of visual ·tion However in advanced stages of the disease secondary vitreo-retinal pl cations such as vitreous haemorrhage and membrane formation preretinal prepapillary fibro-vascular prol ferations and retinal detachment frequently ır These sequelae are then largely responsible for the visual failure

ince some of the complications respond to surgery an ultrasonographic mination using the B scan technique has been advocated when selecting patients vitrectomy (Coleman & Franzen 1974 Jack et al 1974 McLeod et al 1977)

ed June 27 1979

In the present work the gross vitreo-retinal pathology was studied by ultrasonography prior to vitrectomy in a number of diabetic eyes with opaque media and low visual acuity The ultrasonic examination was focused on the demonstration of some surgically important changes such as dense vitreous membranes preretinal and prepapillary proliferations and retinal detachment

Case Material and Methods

During a 20 month period 93 consecutive diabetics (44 males 49 females) with severe vitreo-retinal sequelae and opaque ocular media were examined. Their distribution according to the duration of diabetes is shown in Fig 1 Patients with visual acuity higher than 0 1 were not included in the study By the end of the period 49 of the eyes had undergone a pars plana vitrectomy according to the method previously reported (Algvere 1979)

The ultrasonographic study comprised 168 eyes In 5 patients only one eye was examined The remaining 13 eyes were excluded due to the presence of other disease (or previous enucleation)

Ultrasonography was carried out with a Coleman Ophthalmoscan 100 (Sonometrics Inc New York N Y) using a 15 MHz focused transducer for A-scan and B scan recordings (Coleman 1972) For general topographic information the

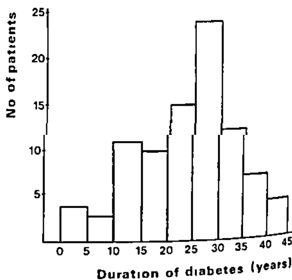


Fig 1

examined using horizontal B scan sections at 2 mm intervals Selected areas scanned in detail When retinal detachments were suspected even sagittal ons were made By adjusting the transducer and the eye high amplitude pendicular) echoes from tissue interfaces were sought The B scan gives an llent topographic survey but yields no information on the intensity of the es A scan echography on the other hand better reveals interfaces of different stic impedance in tissues and therefore this technique also was employed

Results

ous membranes The ultrasonic findings were classified into eight categories two three of which were often present in the same eye (Table I) Dense vitreous ibranes (categories 2 3) were found in the majority of eyes (67%) Posterior ous membranes (category 3) were present in 100 (60%) eyes These membranes located either close to the retina (epiretinal tissue growth) or were retracted riorly into the vitreous space (Fig 2) In 29 eyes posterior vitreous membranes the sole ultrasonic finding but in the remaining cases these were associated fibro-cellular or fibro-vascular proliferations (categories 3 combined with 4 5) and/or retinal detachment (category 6)

ferations Totally 71 (42%) eyes displayed preretinal or prepapillary prolifera s as extraretinal stalks which were usually associated with vitreous membranes

Table I
Distribution of 168 eyes according to ultrasonography

Category	Number of eyes	Category	Number of eyes
Vitreous haemorrhage only	8	2 + 4*	1
Central vitreous membranes	9	2 + 5	2
Posterior vitreous membranes	29	3 + 4	14
Preretinal proliferations	6	3 + 5	28
Prepapillary proliferations	4	3 + 6	13
Localized retinal detachment	20	3 + 4 + 5	9
Total retinal detachment	14	3 + 5 + 6	3
Normal ultrasonogram	3	3 + 4 + 5 + 6	4
		tumour	1

he combination of two or more categories such as 2 + 4 means that both central vitreous ibranes (2) and preretinal proliferations (4) are present



Fig 2

Ultrasonogram showing dense funnel shaped vitreous membranes (at posterior m detached vitreous) adherent to optic nerve head (to the right) Prepapillary stalk is n displayed but was seen at vitrectomy



Fig 3

Prepapillary proliferations recognized at vitrectomy as a fibrovascular stalk from o head



Fig 4
d traction detachment of the retina (arrow) associated with preretinal membranes in posterior pole of fundus Findings verified at vitrectomy

s) As a sole ultrasonic finding such proliferations were thus seen in only 10 tegories 4 5)
-cellular or fibro-vascular proliferations arising from the optic disc (cate *were detected in 50 (30%) eyes (Fig 3) Preretinal proliferations were seen* yes and in most cases originated from the temporal vascular arcades in the or pole

detachment Fifty four (32%) *eyes showed* some type of retinal detachment a localized detachment (Fig 4) and 14 a total one In 20 eyes the retinal ments were associated with ultrasonically dense vitreous membranes (Table gories 3+6 and combinations) Eyes with retinal detachment were classified ing to visual acuity It became evident that the presence or absence of light tion has little if any predictive value for determining the absence or ce of retinal detachment in advanced diabetic vitreo-retinal disease It was r observed that out of the 20 amaurotic eyes 10 had retinal detachments

y of ultrasonography The findings at vitrectomy in 49 eyes provided a useful on the accuracy of preoperative ultrasonography The preretinal prolifera 1 19 and prepapillary proliferatons in 22 eyes (found prior to surgery) turned vitrectomy to be 27 and 33 respectively A correct ultrasonic diagnosis having een made in about 2/3 of these cases In the undetected cases the extraretinal were found at surgery to be associated with posterior vitreous membranes

Table II
Comparison of findings at vitrectomy and ultrasonography
(49 eyes)

Vitrectomy findings	Ultrasonography observations		
	Vitreous membranes	Retinal detachment	
		Localized	Total
Vitreous membranes	26	1	2
Retinal detachment localized	8	12	

and the proliferations were often circumscribed to small areas (less than ... seems that the smaller the stalk the more difficult its differentiation from ... membranes ultrasonically

The most important distinction to be made is that between posterior ... membrane and retinal detachment In this respect the ultrasonic find... verified at vitrectomy in 38 (78%) eyes (Table II) In the 2 eyes wrongly d... as *total retinal detachments the funnel shaped vitreous membranes were* ... that the echoes recorded were similar to those of a retinal detachment

Eight eyes showed only vitreous membranes on ultrasonograms but a... tomy retinal detachments were found as well These were flat detachments lo... to the posterior pole and associated with thick vitreous membranes It ... pointed out that there was a time lapse between ultrasonography and vitr... these 8 cases 2 months in one of them and 5 10 months in the others

Results of vitrectomy in various ultrasonic categories A correlation was found b... the preoperative ultrasonic findings and the vision achieved after vitrec... these eyes the preoperative visual acuity ranged from light projection to ... post-operative visual increase to 3/60 or more was considered an impro... Follow up periods varied between 6 and 24 months (mean 15 months)

Cases with vitreous membranes only and those combined with prep... proliferations showed a postoperative improvement of visual acuity (... in 12 of 20 eyes (Table III) The visual prognosis in eyes with p... proliferations was naturally dependent on the degree of macular ... However it was also substantially affected by the presence of vitreous m...

Table III
Visual results of vitrectomy (49 eyes)

Fraction of eyes	Ultrasonographic categories				
	Vitreous membranes	Prepapill prolifer	Preretinal prolifer	Retinal detachment	
				Localized	Total
proved	5/6	7/14	6/17	4/10	2/?
ichanged	1/6	3/14	6/17	?/10	
teriorated		4/14	5/17	4/10	

ongly diagnosed as retinal detachment surgery disclosed thick posterior vitreous branes postoperative visual acuity 0 4 and 4/60 respectively

prepapillary proliferations In all 4 eyes with localized preretinal proliferations the posterior pole the postoperative visual acuity improved (range 4/60-0 4) On other hand only 2 of 13 eyes with preretinal proliferations combined with ous membranes and/or prepapillary proliferations showed visual improvement al visual acuity 3/60 and 5/60 respectively)

he prognosis in retinal detachment again was influenced by the presence of aretinal proliferations Of 6 eyes with vitreous membranes and retinal detach t 4 reattached and improved following vitrectomy (visual acuity range 0 2-0 4) 4 eyes with retinal detachment combined with prepapillary and preretinal liferations ended up with amaurosis (Table III)

Discussion

vitreo-retinal complications in diabetic proliferative retinopathy are likely to e severe visual loss It was reported (Beetham 1963) that approxiamately 30% iabetics with proliferative retinopathy were legally blind and that 40% of eyes such retinopathy had a visual acuity of less than 0 1 (Madsen 1971a)

he present study shows that ultrasonically dense vitreous membranes are seen 7% of eyes with such low visual acuity These are comparatively thick structures incidence of thin membranes or strands is certainly much higher since only ctures of some ultrasonic density are clearly displayed with the method used In experience even optically dense (yellow-ochre) opacities may escape B-scan

detection The absence of echoes from long standing vitreous haemorrh known also from A scan studies (Oksala 1963)

The preretinal and prepapillary proliferations were associated with the vitreous changes in a high percentage (87%) This again emphasizes the vitreous contraction (Davis 1965) and lends support to Machemer's sug (1978) that mechanical factors are involved in the pathogenesis of proli retinopathy

The development of retinal detachment in proliferative retinopathy is known and crucial event (Tolentino et al 1966 Tasman 1972) The preval retinal detachment in such retinopathy (245 eyes) was reported to be 21% 1971b) In the present series about 1/3 of the eyes had ultrasonic evid retinal detachment Even if the diagnostic criteria for B scan (Coleman 1973) are combined with those for A scan localized traction detachments retina may be difficult to demonstrate This seems particularly the case whe retinal detachments are associated with thick posterior vitreous membrane vitreo-retinal adhesions (Algvere et al 1978) Accordingly our observ vitrectomy showed retinal detachment in 41% of eyes Amaurotic eyes reveal half of the cases studied Thus with progression of the diabetic disease incidence of retinal detachment increases considerably

The accuracy of ultrasonic diagnosis of retinal detachment was 89% progressive vitreo retinal disease the development of such detachment is and may in some eyes have occurred during the time interval between ultra graphy and vitrectomy If so our diagnostic error would decrease In 94 di Jack et al (1974) found an overall accuracy of ultrasound in determining the status to be 85%

Ultrasonography yields valuable information on the visual prognosis vitrectomy Thus 60% of eyes with vitreous membranes and prepapillary pro tions showed postoperative visual improvement (range 0 1 0 9) Preretinal pro tions in the posterior pole when associated with vitreous changes showed improvement in only 2 out of 13 cases Retinopathy in such cases is genera severe In addition preretinal proliferations often have broad vitreo-retinal ons and are difficult to excise and when persistent cause tangential retinal tr and detachment

References

Algvere P (1979) Vitrectomy after intracapsular cataract extraction in diabetic sequ *ophthal (Kbh)* 57 530–542

Algvere P Epstein D Jerneld B & Linde C J (1978) Det tvådimensionella ultral genom ogat Erfarenheter av ultrasonografi B scan vid intraokular diagnost *Läk gen* 75 422 425

am W P (1963) Visual prognosis of proliferati e diabetic retinopathy Brit J Ophthal 611–619
ian D J (1972) Reliability of ocular and orbital diagnosis with B scan ultrasound I ilar diagnosis Amer J Ophthal 73 501–516
ian D J & Franzen L A (1974) Vitreous surgery Preoperative evaluation and gnostic value of ultrasonic display of vitreous hemorrhage Arch Ophthal (Chicago) 92 –381
ian D J & Jack R L (1973) B-scan ultrasonography in diagnosis and management of nal detachments A ch Ophthal (Chicago) 90 29–34
M D (1965) Vitreous contraction in proliferative diabetic retinopathy Arch Ophthal. icago) 74 741–751
R L Hutton W L & Machemer R (1974) Ultrasonography and itrectomy Amer J thal 78 265–274
emer R (1978) Pathogenesis of proliferative neovascular retinopathies and the role of ectomy A hypothesis Int Ophthal. 1 1–3
en P H (1971a) Prognosis for vision and fundus changes in patients with proliferative betic retinopathy Brit J Ophthal 55 372–38?
en P H (1971b) Orular findings in 1?3 patients with proliferative diabetic retinopathy um ophthal. 29 351–374
od D Reston M & Wright J E (1977) Rapid B scanning of the vitreous Brit J Ophthal. 437–445
a A (1963) Experimental and clinical observations on the echograms in vitreous norrhages Brit J Ophthal. 47 65–70
ian W (1972) Retinal detachment secondary to proliferative diabetic retinopathy Arch thal (Chicago) 87 286–289
itino F I Lee P F & Schepens C L (1966) Biomicroscopic study of vitreous ca ity in betic retinopathy A ch Ophthal (Chicago) 75 238–246

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THE VARIABLE ANGLE MIRROR A NEW TOOL FOR THE STUDY OF OCULAR DOMINANCE AND EYE FIXATI

BY

ÅKE BJÖRK

A simple tool for studying optical dominance consisting of two plane mirrors moveably fixed to one another was developed The patient looks stra ahead at the reflection of his own face and observes which eye is covered by the joint between the two mirror halves By changing the angle a further checkup on eye dominance can be obtained The method is simple and gives us a quick idea of the eye dominance

Key words Binocular vision – dominance tests – ocular dominance strabismus

Most people are right handed and right footed This function of limbs is contro by the contralateral cerebral hemisphere The eye is different The partial de tion of the optic fibres at the chiasm links each eye with both hemispheres know however that some sort of ocular dominance really exists in a sma greater part of the general population and can be tested in various ways (Fink Coren & Kaplan 1973 Dawson 1949)

Finding reliable tests to point out the dominant eye is difficult Many kind tests are available but many of them test different factors which explains wh agreement between tests is often poor Michaels (1972) has contributed an excellent critical review of the whole field of ocular dominance

Here is described a new test method that seems to have a decided advantage conventional tests for ocular dominance

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Methods and Material

'Angle Mirror Test

variable angle mirror (VAM) consists of two plane glass mirrors attached to another by a hinge along the intersection line The size of the mirror should be e enough to enable the patient to see the whole of his face The mirror is placed a table about 0 5 m in front of the patient like an open book the two glass-plates ming an angel of 90° The patient looks straight ahead at his own face keeping h eyes open He is told to ignore the joint between the two mirror halves which isible like a vertical line before the image of the face It is important that the ire face is equally illuminated otherwise the result may not be valid A piece of oured tape is stuck to each of the patient s ears and sides are referred to as e g or green instead of right and left to avoid confusion The patient can be asked orrect the angle by looking at his own face and by making small adjustments of mirror halves The patient is asked if the vertical line covers his red or his green By moving his head a bit to the right and then to the left he often has a better ince to observe the dark line Three different situations are possible The line is front of the image of the right eye or of the left eye or the patient observes two s one before each eye The two first conditions point out right-eyedness and t-eyedness respectively (Fig 1) The patient seeing two lines at the same time



Fig 1
A left-eyed person s view of herself in the angle-mirror



Fig 2
The same situation as in Fig 1 but after having increased the angle of the m rror



Fig 3
A person s view of herself with the left eye covered



Fig 4
The same situation as in Fig 3 but the angle of the mirror is increased

tes no marked supremacy of either eye he is ambiocular In this group there everal intermediate forms and we should note tendencies to right or edness e g *the patient declares that he can see two lines one of which is* r and may disappear for a while

other method using the mirror – still at the trial stage – is to ask the patient to ise the angle between the mirror halves when looking at his face and continue djustment until the face seems compressed and only one eye is visible in the r (Fig 2) With the mirror still in this position the patient is asked to look in ier direction *in the room and then into the mirror again If the same eye is* it every attempt then it is most probably the non-dominant eye

er there are some problems involving reliability of this last mentioned od that have not yet been fully solved We hope to tackle these and present ts at a later date

at it is really the image of the dominant half of the face that is suppressed can ustrated by covering one eye of the subject when using the WAM (Figs 3 and

order to elucidate the question in which extent the results from the WAM test spond with a sighting test 28 subjects were tested The results (Table I) ate good correlation between the two methods

Subject age and sex	Visual acuity and refraction	Heterophoria (Herschel s variabel prism with the Maddox groove 5 m)		Stereovision (Titmus)	VAM test	Sighting test
CM 12 M	RF 1 0 (−1 50) LE 1 0 (−1 25)	Exoph 1	0	n	R	R
ER 20 M	RE 1 5 (+1 50) LE 1 25 (+2 0)	0	0	n	R	R
SK 20 M	RE 1 5 (−3 25) LE 1 5 (−3 50)	0	Hyp 0 5	n	R	R
IJ 13 F	RE 1 5 (+0 50) LE 1 5 (+0 50)	Exoph 1 0	0	slight defect	R	R
CK 34 M	RE 1 5 (−1 25) LE 1 0 (−1 75)	Esoph 1 0	0	n	R	R
VB 5 F	RE 5/3 LE 5/3	–	–	n	R	–
SM 25 M	RF 2 0 (±0) LE 1 25 (±0 sph −1 2 cyl 0)	Esoph 0 5	0	slight defect	R	R
SC 16 M	RF 2 0 (−1 0) LF 2 0 (−1 5)	0	0	n	R	R
BÅ CM	RF 1 (±0sph+0 75cylx95°) LE 1 (±0 ph+0 0cylx90°)	Exoph 1 5	0	n	R	R
BS 55 M	RE 1 (+0 25) LE 1 (+0 0 [illegible] +0 ylx175°)	Esoph 0 5	0	n	R	R [illegible]

	LF 1 5 (+0 75)					
OI 27 F	RF 2 0 (±0) LE 1 5 (±0)	Fxoph 0 5	Hyp 0 5	n	RL	RI
BO 32 M	RE 1 25 (±0) LE 1 5 (−0 25)	Fxoph 1 0	Hyp 0 5	n	RL	RI
EP 20 M	RE 1 0 (−7 0) LE 1 25 (−7 25)	–	–	n	RL	RL
JI 59 F	RE 1 0 (−3 0) LE 1 0 (−3 0)	Fsoph 7 5	0	n	RL	RL
LT 65 M	RF 1 5 (+1 0sph−0 5cylx80) LF 1 5 (+1 0sph−0 5cylx95)	0	0	n	RL	RI
LM 33 F	RF 1 5 (+0 50) LE 1 5 (+0 5)	Exoph 0 5	–	n	RI	RI
CL 9 M	RE 1 5 (±0) LE 1 5 (±0)	Fsoph 0 5	0	n	l	RI
SF 23 F	RF 1 5 (−1 75sph) LF 1 5 (−1 75sph−0 5cylx90)	Fsoph 2	0	n	L	l
JB 35 M	RE 1 5 (+0 25) LF 1 25 (+0 50)	Exoph 0 5	0	n	L	l
BF 63 F	RF 1 5 (+1 0) LE 1 0 (+1 25)	0	0	n	Rl	R
OM 27 M	RF 1 5 (+0 50) LF 1 5 (+0 50)	Fsoph 5	Hyp 0 5	n	Rl	Rl
BC 31 F	RE 1 5 (−0 75) LF 1 5 (−0 50)	Fxoph 0 5	0	n	Lr	l

R = right dominance l = left dominance RL = ambiocular Rl = right dominance sometimes ambiocular
Lr = left dominance sometimes ambiocular n = normal

Results

One of the results of tests with the VAM method was that quite a few subje- not show a dominant eye. This raises the question of the differentiating capa- the method itself. This is why a comparison with a sighting method seemed s... Our method is a modification of the so called Visierversuch (Hamberger Sachsenweger 1969 and others).

Our procedure can briefly be described as follows.

The patient is told to keep both eyes open and hold a ruler with both hands and bring alignment with a distant object. To perform this operation the patient uses only one e- being conscious of which eye he has chosen. By placing a card in front of the patient' eye and then in front of his left eye we can quickly get an answer which eye is the sighting eye. If the subject for example has used the right eye for taking aim he is right dominant or ambiocular. Covering the right eye now forces the subject to aim w left eye. If on uncovering the right eye the left can maintain the alignment he is amb. If however the right eye takes over the subject is right-dominant. This is repeated three times.

At this stage it can be mentioned that the agreement between the VAM-test a- above described sighting method is excellent if adequate subjects can be Quantitative results will be presented in a future article (see also *Table I*).

Discussion

The VAM test is a new simple method for determining the dominant eye ... obvious advantages. The subjects often feel motivated to a great extent. Th... and the subject's own face is something which compels attention from oth- uncommunicative patients. The mirror can therefore be used in cases where methods might fail as with children. The fact that the subjects are ignorant ... purpose of the examination is an advantage and moreover they have no ... taking part in a sighting operation. They themselves cannot judge what is ... *left in the mirror* thus giving results probably more reliable than those of ... sighting method.

The sighting method requires more instruction than the mirror method ... training in similar circumstances as when aiming a *gun* could contribute ... perhaps incorrect opinion on the eyedness. The sighting operation is ... uncertain and vacillating.

Swift and accurate establishment of eye-dominance is of clinical interest ... authors have pointed to various fields of practical application (Sachsenweger and others). Reference has been made to the importance of knowing which is ... dominant eye before glass correction of anisometropia. It is considered that ...

e eye with reduced vision is more troublesome when affecting the dominant

cases of strabismus with very small deviation angle it can be difficult to decide i is the fixating eye and whether an alternation exists The mirror method s to be a usefui tool in such circumstances as has been shown in some minary tests in our laboratory

this connection the question has been raised as to how early in childhood eye nance is established and to what extent it changes during the period of growth furthermore how strong a reduction of vision will result in the loss of nance

oking into a mirror when writing writing reversed script without using a or and similar things in relation to the question of eyedominance have long a popular field with psychologists It is hoped that the VAM method will ibute some details of psychological interest.

References

i S & Kaplan C P (1973) Pattern of ocular dominance *amer J Optom 50* 283–29?
r B (1944) A battery of tests for the dominant eye *J gen Physiol 31* 179–190
on H (1949) The Physiology of the Eye 1st ed London J & A Churchill Ltd (cited by ren S & Kaplan C P (1973) *amer J Optom. 50* 284)
N H (1938) The dominant eye *A ch Ophthal (Chicago) 19* 55–58?
berger F A (1943) Uber monokulare Dominanz im binokularen Sehakt. Klin Mbl genheilk 109 1–11
iels D D (1972) Ocular dominance *Surv Ophthal 17* 151–163
enweger R (1969) Die klinische Bedeutung der monokularen Dominanz *Docum thal. 26* 273–278

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PATTERN CONTRAST THRESHOLDS IN LATE

BY

RICHARD V ABADI

The evaluation of motor and sensory responses in indi nystagmus is described Under monocular binocular and conditions subtle differences in interocular contrast sensi strated A simple afferent model is proposed to acco nystagmus

Key words latent nystagmus – contrast sensitivity – mon and dichoptic viewing – E O G

In some individuals it is possible to generate involuntary osc occluding either eye This condition is known as latent nysta reported over one hundred years ago by Faucon (1872) nystagmus is horizontal and jerky in form with the fast ph open eye

Many studies suggest that the aetiology of the disorde genetic influences appear to exist (Kornhuber 1960) Fro Anderson (1954) Crone (1954) and Jung & Kornhuber (1 may be considered as part of an oculomotor syndrome - concomitant) and an alternating hyperphoria being th Conversely Jung & Kornhuber (1964) state that about 15% latent nystagmus

Because of the nature of the nystagmus and the mechan evoked (i e by covering one eye) the clinician quite natur difficult to assess such fundamentals as monocular visual a aim of this paper to describe the detailed investigation

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ıonal psychophysical techniques Contrast sensitivity functions (CSF) of the ːr will be examined under monocular dichoptic and binocular viewing ɔns thus revealing the subtle differences in interocular spatial vision rmore the effect of monocular blur and a controlled change in monocular ıel on spatial thresholds will provide a qualitative description of the effect of tagmus on the detection of stationary contours

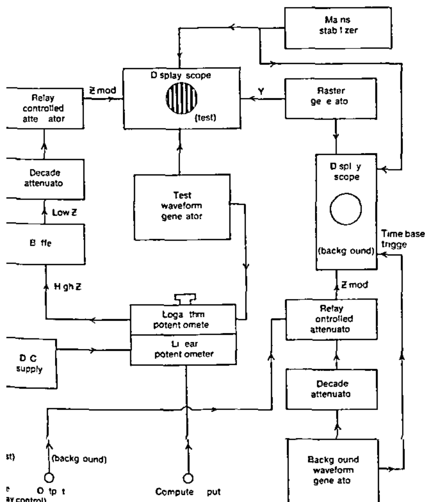


Fig 1
Schematic arrangement illustrating the circuit layout for the generation of the grating pattern

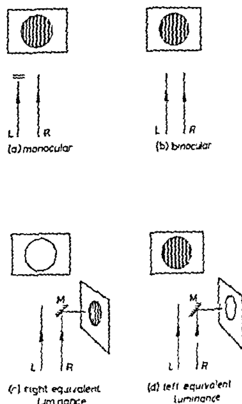


Fig 2

Schematic arrangement of the four different viewing conditions L, R and M ... right eye and mirror respectively

Methods

(a) Sensory Tests

Contrast sensitivities were assessed by determining the contrast threshold ... sinusoidal gratings of different spatial frequencies (Schade 1956 Campbell & ... Abadi 1974 Arden 1978) The patterns were generated electronically on the ... Solartron CD 1400 display oscilloscope (Phosphor P31) and a second ... provide a second field of an equivalent luminance to that of the first display (Fig 1 ... eye could view a patterned field while the other viewed a field of equal bright... different viewing conditions were used to examine the visual response monoc... binocular (Fig 2b) and equivalent luminance (Figs 2c d)

Contrast thresholds were found by the subjects adjusting a calibrated logarithmic potentiometer until the vertical sinusoidal grating pattern could just be detected ... was then repeated ten times at different spatial frequencies In this study spatial ... defined as the number of cycles per degree of visual angle and contrast as (L_{max} ... + L_{min}) where L_{max} is the luminance at the centre of the bright bars and L_{min} the ... at the centres of the dark bars The resultant threshold curve may be described ...

ast sensitivity function (CSF) where contrast sensitivity is the reciprocal of contrast ld CSFs were determined for all four viewing conditions (Fig 2a–d)

ffect of a uniocular luminance change while the other eye viewed a 2 5 c/deg vertical lal grating was examined by placing neutral density filters over the left eye lar threshold responses were found for each graded increase in monocular retinal nce the subjects being initially dark adapted for 25 min

circular display field subtended 7° in diameter at a viewing distance of 57 cm Using a posure photometer the pale green displays were calibrated to have a space average nce of 6 cd/m² Subjects fixated a central spot on the displays during the experiments l patterns were used because the direction of the LN was horizontal and would uently degrade the detection sensitivity maximally at this orientation (Abadi & rioglu 1975)

tor Tests

nonitoring of the direction amplitude frequency and velocity of the nystagmus was d by using the electro-oculogram (EOG) The skin was cleaned with acetone prior to plication of Cambridge electrode gel and the Ag AgCl skin electrodes were secured trically about the canthi in the horizontal plane and the reference electrode was placed forehead When the eyes moved a signal was passed through DC amplifiers and a filter width up to 30 Hz) and then monitored on a chart recorder One degree of eye ient was approximately equivalent to 20 μV (Abadi & Sandikcioglu 1974) Recordings ken both during the experiments and also independently of the psychophysical tasks

bjects

gh three subjects were examined in detail the data from only one of the subjects will ribed and commented on since all three showed similar responses It is interesting to hat observers S A (V A 6/24 6/6) G T (V A 6 6 6 6) and C S (V A 6/18+ 6/18+) ed to different visual acuity groups The primary representative subject for this study S (25 years old) *in whom LN was first noticed at 3 years of age and who had no* tic treatment or ocular operation in the past Her present refraction revealed OD −2 25 × 40 6/18+ OS +4 50 −3 50 × 175 6/18+ Binocular V A 6/12−
di and media normal Orthoptic examination revealed an alternating hyperphoria as a latent nystagmus On covering one eye both eyes broke into a conjugate jerky ntal nystagmus with the fast phase towards the open eye and with the eye under cover g up

two control observers were E. E L an emmetrope and R. V A a corrected myope

Results

can provide much information about visual processing for they represent a nient means of describing both the sensitivity and the projected resolution of ecting system Typical normal curves are illustrated in Fig 3 Here monocular dichoptic (●) and binocular (o) CSFs show the familiar low (<3 0 c/deg) and (>8 0 c/deg) attenuation in sensitivity The linear abscissa and logarithmic nate correspond to spatial frequency (c/deg) and contrast sensitivity respective

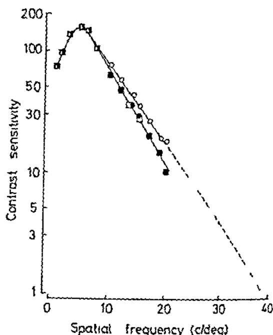


Fig 3
A contrast sensitivity function (CSF) for a normal observer viewing vertical gratings either monocularly (□) right equivalent luminance (●) or binocularly log/linear co-ordinates the functions may be extrapolated (broken lines) to pr resolution limits for the viewing conditions

ly With these coordinates the CSF becomes linear from around 8 c/deg on Extrapolated regression lines to unity contrast sensitivity will provide an es of the ultimate resolution that may be achieved when viewing a sinusoidal target of 100% contrast For the control observer E E L the resolution f monocular and dichoptic viewing was 34 c/deg as compared to the somewha value when two eyes were used (39 c/deg)

On the other hand quite dramatic differences are noticed for the subject As expected the binocular sensitivities are much lower than normal (Fig interestingly the shape of the whole function is linear with no low f attenuation Genuine indications of monocular vision are illustrated in F 6 Here sensitivity responses for dichoptic viewing provide the precise assessments of vision Right equivalent luminance (Fig 2c and Fig 5) pattern input enters the right eye only and an equivalent luminance fiel provides a curve almost identical to that for binocular viewing (compare Fi 5) whilst left equivalent luminance shows a less sensitive function (Fig 6) T right eye is not only the more dominant but also the more sensitive

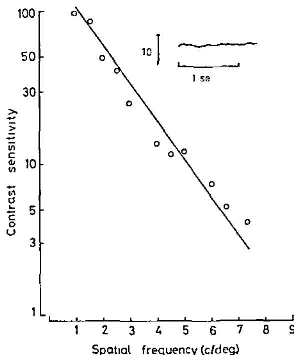


Fig 4

…or binocular viewing of vertical gratings The subject has a latent nystagmus (LN) Inset shows no eye movement response

…s traces show no sign of LN under these ideal conditions If however no care is …n to provide matching background luminance fields and traditional monocular …itions prevail then a coarse LN comes into play reducing the CSFs for both the …t and left eyes (see insets (b) of Figs 5 and 6)

…nly one threshold point could be determined for left monocular viewing (Fig 6 …) due to the large resultant nystagmus on occlusion of the contralateral eye …s contrasts with the uniocular performance of the right eye (Fig 5 –□) Not …risingly the EOG traces indicate that the induced nystagmus has a greater …plitude and frequency in the less dominant eye

… far it has been seen that by providing a dichoptic equivalent luminance …ngement no or little embarrassment of the oculomotor system is achieved But …e highest form of dissociation monocular occlusion is attempted disorder …ails The question arises as to what factors are responsible for the introduction …e nystagmus?

…ne possible answer to this is expressed in the form of Fig 7 Here the LN is seen

to be induced in a controlled manner by changing the ambient illumina eye only thus providing a continuum from monocular to binoc Moreover the threshold data points are compared with those during bi and monocular (M) viewing with unilateral blur from a + 10 D sphere a effect of head posture and its attendant compensatory conjugate ve movement By using a low spatial frequency test grating (0 5 c/deg) a luminance levels the thresholds for the eye under test (i e the right within standard errors unaffected by the very small pupillary changes the neutral density filter s cover of the contralateral eye

In Fig 7 the monocular reduction of luminance (abscissa) is plot contrast sensitivity (ordinate) for two observers a control and the observ As the luminance is reduced in one eye from a factor of 0 to 3 log units, threshold is measured while the subject views a 2 5 c/deg vertical sinew The control observer on progressing from a zero to a 1 95 log unit change moves from binocular (B) to monocular (M) viewing

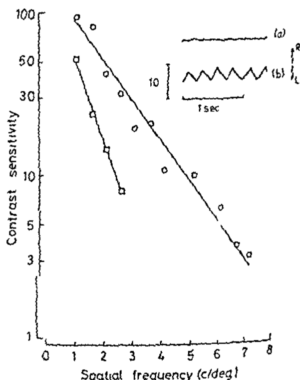


Fig 5

CSF for right equivalent luminance (O) and right monocular (□) viewing of vertical Subject has a LN Inset shows right beating jerky nystagmus only present d monocular task (b) and not during equivalent luminance (a)

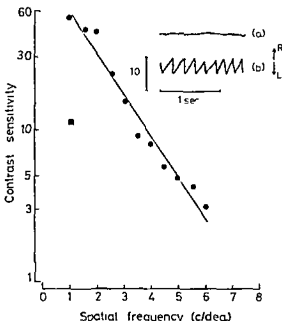


Fig 6

for left equivalent luminance (●) and left monocular (■) viewing of vertical gratings ct has a LN Inset shows left beating jerky nystagmus only present during left monocular task (b) and not during equivalent luminance (a)

ny further monocular luminance reduction has no effect on the contrast itivity A similar relative change also occurs for the latent nystagmat between e values However as the luminance is gradually reduced further sensitivity inues to fall until at a factor of 2 5 log units the sensitivity remains constant os of the sensitivities for the control versus the nystagmat are given by the open es symbols (o)

a + 10D sphere is placed before the left eye (i e equivalent to right eye nocular vision) then the contrast sensitivity is shifted by a factor of 1 6 which is iter than the reduction in sensitivity due to monocular occlusion with a 1 25 log neutral density filter If the left eye is completely occluded then there is a trast sensitivity drop of a factor of 5 (Fig 5) However if the open eye is ucted by either converging or turning the head to the right the contrast sitivity drop is only by a factor of 2 (broken arrow ——→) That is adduction of open eye or convergence dampens the nystagmus

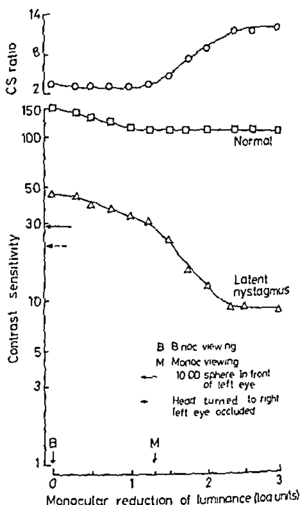


Fig 7

The effect of a unilateral change of luminance on the binocular contrast sensitivity for viewing 2 5 c/deg vertical gratings Contrast sensitivity (CS) ratio for the two eyes also shown Observer with LN △ Control □ See text for details

Discussion

Eye dominance may be expressed in two different experimental mode and sensory For all three subjects the less dominant eye displayed a intensity (amplitude × frequency) of nystagmus than its fellow when each target monocularly in turn The sensory tests yielded the same result in that for the dominant eye showed higher sensitivity values over the whole frequency range For normal individuals this would not be the case each approximately equivalent in sensitivity and exhibiting no relative oscillation

is interesting to note that the shape of the CSF for the nystagmats showed no frequency attenuation This is most probably due to the induced temporal ements of the retinal image making it less likely that the low frequencies are ilised and thus fade (Kulikowski 1971)

ve movement phenomena are rarely simple to understand and L N is no ption Classically L N occurs during uniocular fixation although this present y has shown that if the other eye is viewing an equivalent luminance field then nystagmus will occur Yet any embarrassment of the binocular state by either al blur or a luminance difference induces a jerky nystagmus and a subsequent wered contrast sensitivity Moreover niether of these two conditions (i e + 10 0 phere or a 1 25 log unit uniocular attenuation of luminance) which effectively nsfers vision from a binocular to a monocular state reduces the sensitivity of the em to its true monocular state Apparently this can only be achieved by nocular occlusion or a large interocular luminance difference – in this case 2 25 units

hat then initiates the L N? Consider that the incoming monocular visual inputs er a binocular comparitor housed in the cortex If the two signals are equal a o potential results providing no excitement to either of the two monocular trol systems i e right eye and left eye If however the two signals are unequal n either a positive (for the right eye) or a negative (for the left eye) signal will be rated thus indicating which of the two should take up fixation since true ocular vision will be inhibited In normals the inter monocular switching chanism functions adequately to provide feed back to control the oculomotor em For the observer with L N the feed back produces an instability resulting in a jugate drifting of the two eyes In order to reset the now unbalanced conjugate e a rectifying saccade is initiated Thus the familiar jerky nystagmus results It st be remembered that although the use of threshold patterns during the hoptic experiments did not induce a L N a high contrast pattern (40%) did uce a L N in the observer suggesting that the control system must also include ne sort of visual threshold device

Although this argument may be essentially thought of as an afferent theory van et (1973) has proposed that even more central mechanisms may be responsible leed using a most ingenious technique he has been able to describe some cases ere subjects who had L N could induce the jerky oscillations by the intention of king with one eye That the patient is required to consciously suppress vision in e eye while fixing with the other is not a particularly difficult task considering t the presence of such anomalies as alternating hyperphorias/tropias and rizontal strabismus are not uncommon in these individuals Thus the central tching reported may be a secondary development to the motor deviations

Acknowledgements

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References

Abadi R V (19 4) V sual analys s w th gratings Brit J phys Op s29 49 56

Abad R V and Sand kcioglu M (1974) Electro Oculograph c respon es n a case of Id opath c Nystagmus *Brit J Ph Optics 29* 73–8

Abad R V & Sand kc oglu M (1975) V sual resolut on n congen tal pendula r
Amer J Optom 52 573 581

Anderson J R (1954) Latent nystagmus and al ernat ng hyperphoria *Brit J O*
17 231

Arden G B (1978) The mportance of measur ng contrast sen v n cases of d sturbance *Brit J Oph hal 62* 198 209

Campbell F W & Green D G (1965) Opt cal and ret nal factors affect ng nal res
Phy ol 181 6 5 593

Crone R A (1954) Alternating hyperphoria *Brit J Oph hal 38* 591 604

Faucon A (1872) Nystagmus par nsuff sance des dro t ex ernes *J Ophthal* (P n 1

Jung A & Kornhuber H (1964) Results of electro nystagmograph n m n The optokinet c vest bular and spontaneous nystagmus for neurologic diagno s and me In *The Oculomotor S tem* Bender M (ed) pp 4 8 488 Harper & Row New Yo k

Kornhuber H H (1960) Über Begle sch elen Und Laten en Ny tagmus A Neurolog S cht *Proc Ve e n Rhe n h We fäl her A genarzte 107* 45 48 Verlag Z Balve

Kul kowsk J J (1971) Effect of eye mo ements on the con rast sen it v of pattern patterns *Vi on Re 11* 261 273

Schade O H (1956) Opt cal and pho oelectric analog of the e e *J Op 5*
721 739

V het A G M van (1973) On the central mechan sm of la ent n stagmus A ta
51 772 781

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THE OPTICS OF STATIC PHOTOGRAPHIC SKIASCOPY

Comments on a Paper by K Kaakinen

A Simple Method for Screening of Children with Strabismus Anisometropia or Ametropia by Simultaneous Photography of the Corneal and the Fundus Reflexes

BY

HOWARD C HOWLAND

The appearance of reflexes in static photographic skiascopy is a function of myopic or hyperopic focus of the subject relative to the camera camera to subject distance subject pupil size distance of flash relative to optic axis and camera aperture stop This paper specifies this function

Key words static skiascopy – fundus reflex – photography screening of vision defects and eye disorders in young children

[Rec]ently Kaakinen (1979) reported a method for the simultaneous photography of [cor]neal and fundus reflexes using a 35 mm camera and flash unit mounted on the [peri]phery of the lens The technique has the advantage that a great deal of [info]rmation about eyes is recorded instantaneously in a single photograph As a [met]hod of refraction however it leaves something to be desired in that only one [mer]idian of each eye is refracted at a time Further for a range of relative refractive [err]ors centered about perfect focusing on the camera no reflex is seen and hence [nothing] can be inferred about the refractive state of the eye except to say that it is [with]in a certain dioptric range of the correct focus Moreover this range of relative [dio]ptric defocus is a function of the pupil radius of the subject r the distance of the [flas]h from the optic axis passing through the center of the camera aperture and [sub]ject s pupil h the radius of the camera aperture itself c and the camera to [sub]ject distance d The purpose of this note is specify this function

[Rece]ived October 16 1979

Optics of Static Photographic Skiascopy

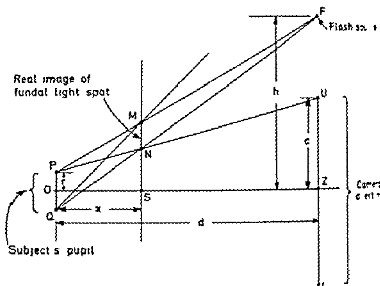


Fig 1

Optics of static photographic skiascopy The space between the subject and the c depicted The flash is located at point F at a height h above the optic axis passing the center of the camera lens UZL and the center of the subject s pupil POQ The focused myopically relative to the camera at a distance x from his pupil where distance from the camera to the subject A real image of the illuminated spot on the retina is formed at MN since the entering rays FMP and FNQ must also return from the pupil from P to M and Q to N respectively The horizontal distance of MNS x has been chosen so that the ray through PN will just enter the camera aper upper edge at U causing a crescent to appear on the pupil photograph The poi located by solving the simultaneous equations for the two lines PNU and QNF and of x thus obtained

Method

In Fig 1 is illustrated the geometry of the static photographic skiascopy subject is (myopically) focused on a plane between the camera and himself

In this situation the out-of focus image of the flash on the retina the fl treated as a point source F in the plane of the camera aperture must be that the subject is focused at a plane in front of the camera at a distance x of his pupil

At this plane the retinal image is re imaged in a circle whose diamet section is MN Note that each point on MN is illuminated by rays com

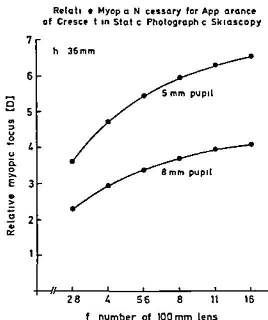


Fig 2

…ive myopia necessary for appearance of crescent in static photographic skiascopy It is …ned that the flash source is located 36 mm above the optic axis The region above each … designates the combination of f numbers and relati e myopia in which an illuminated crescent will appear in the photograph of the subject s pupil

…ions of the subject s pupil PQ but shown are only rays from the extreme edges …e pupil

… the plane MN is sufficiently close to the subject s pupil i e if the subject is …iciently myopic then a ray from the upper edge of the pupil passing to the …r edge of the real image PN may just enter the top of the camera aperture at …t U In this event a crescent will appear in the picture of the subject s pupil

…rom the diagram it is clear that the subject s pupil radius r the radius of the …era aperture c the height of the flash from the optic axis h and the focus …ance of the subject x all play a role in determining whether or not a crescent … be seen By writing the equations for the lines PNU and QNF in terms of a …rdinate system centered at 0 in the subject s pupil POQ and solving for the …rsection N of the two lines in terms of x it is possible to show that a crescent … be seen when

$$x \leq \frac{2rd}{2r + h - c} \qquad (1)$$

Similar ray trace diagrams for relative hyperopic focusing by the subject ie

$$x \gtrsim \frac{2rd}{c-h+2r}$$

It will be noted that if (c h) < 2r then the subjet must be absolutely hyper that a virtual image is formed behind the eye (x < 0) before a crescent will be

To illustrate the effect of the size of the camera aperture Fig 9 shows the of relative myopia which the subject must exhibit before a crescent is se pupil photographs for two pupil sizes as a function of f number stop of the for a 100 mm lens (suggested by Kaakinen 1979) for a separation of the fla mm from the optic axis It will be seen that at small pupil sizes and large f the method is quite insensitive to significant degrees of myopia

Discussion

It is clear that if one wishes to use static skiascopy as a screening method carefully set the parameters of the optical system so as to be able to detect refractive errors in the pupil sizes encountered in the test

This implies that careful track must be kept both of subject pupil size (w be measured from photographs) as well as the aperture size used in the cam

In contrast to the method proposed by Kaakinen (1979) which em eccentric flash source refracts a single axis at a time and has a large refrac zone in which little information about refractive error is obtained one ma employ a refractive method with a centered fiber optic probe in which mul can be refracted simultaneously and which has a very small refractive de (Howland & Howland 1974 Howland et al 1978) Admittedly however method does not permit the simultaneous recording of corneal reflexes

Acknowledgment

A portion of this work was supported by Grant EY02994-01 from the National Ey Health I am greatly indebted to Prof R Weale Institute for Medical Optics Lo allowing me to work in his laboratory on related problems in the optics of pho refraction I thank M Howland for drafting the figures

References

Howland H C & H wland B (1974) Photorefraction A technique for stud of stare at a distance *J Opt Soc Amer 64* 240–249

Howland H C Atkinson J Braddick O & French J (1978) Infant astigmatism mea photorefraction *Science 202* 331–333

-en (1979) A simple method for screening of children with strabismus anisometropia metropia by simultaneous photographs of the corneal and the fundus reflexes Acta al (Kbh) 52 161–171

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Reply to H C Howland s Comments

BY

K KAAKINEN

Howland s geometrical analysis of the optics of the static photographic opy is illustrative from a theoretical point of view However I would like to iasize that I have studied the static photographic skiascopy only in practice reliability of my method has been tested by Kaakinen (1979) and Kaakinen & mila (1979) in standard circumstances which are somewhat different from the etical analysis of H C Howland

ie distance (h) between the optical axis of the camera lens and the center of the is 25 mm instead of 36 mm and the distance of the lower edge of the flash ctor to the optical axis of the lens is only 15 mm If 15 mm is used as h the culation of the curve then indicates that a minimum myopia refraction of 2 25 ters (with an 8 mm pupil) would produce a crescent with average value of mbers 11 and 16 which I have constantly used depending on the sensitivity of ilm

owever it should be emphasized that in H C Howland s geometrical analysis lash lamp has been taken as a point source of light Clearly the flash lamp is a t source as far as the corneal reflex is concerned but H C Howland s ment is chiefly with the retinal reflex In this latter case exception might be n in treating the flash as a point source since with respect to the other ensions used in the geometrical analysis (e g camera aperture radius 13–2 5 pupil diameter 5–8 mm and distance between light source and optical axis 36

mm 25 or 15 mm) the reflector of the flash lamp is large being 90 mm 33 mm wide Moreover to be completely accurate treatment of the flash extended source should also take into account the fact that light emma is divergent

From experiences in practice it is well known that the sensitivity of the dependent on the distance of photography and the distance between f and the optical axis of the camera lens The influence of the pupillary sensitivity of the method for refractive errors is also mentioned in the articles and therefore the photographs have been taken in dim light plepic medication has also been recommended

The small influence of the different sizes of the apertures of the camera the sensitivity of the method for refractive errors is apparent in the photo the demonstration eye Therefore in the clinical studies the aperture 11 and 16 only had been used

As mentioned in clinical reports it is true that the method is rather inse small refractive errors and only one meridian (vertical) is measured

However the method can be made more sensitive as desired by using medication or by increasing the distance of photography (d) or by dim distance between the flash light and the optical axis of the camera lens using small aperture numbers (f)

Other meridians can also be measured by turning the flash light to positions on the side of the lens because the method measures the refrac line through the camera lens and the light source Further the prelim with a partly covered ringflash appear promising in obtaining specific astigmatic errors

The method is most suitable for screening strabismus and high refrac Its accuracy is most sufficient for exact refraction measurements but developed further Worthy of consideration is the fact that method is for anyone to construct and use Considering the simplicity of the functions surprisingly well in the screening of small children with stra HIGH refractive errors or anisometropia

There is no doubt about the superiority of the excellent method of H Howland (1974) as a refractive technique (US patent 3879113 (A 61 B which multiple axes can be refracted simultaneously with a very small dead zone But technically the apparatus and the procedure is more co and the evaluation of results with it is more complex

References

d H C. & Howland B (1974) Photorefraction A technique for study of refractive
it a distance *J opt. Soc Amer 64* 240–249
:n K (1979) A simple method for screening of children with strabismus anisome-
i or ametropia by simultaneous photography of the corneal and the fundus reflexes
phthal (Kbh) 57 161–171
:n K & Tommila V (1979) A clinical study on the detection of strabismus
metropia or ametropia of children by simultaneous photography of the corneal and
indus reflexes *Acta ophthal (Kbh) 57* 600–611

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ENUCLEATION IN CHILDREN

BY

INGRID AXELSEN and NIELS EHLERS

In adults enucleation is usually considered a rather simple operation. In contrast the removal of an eye of a child is often a difficult task. We describe an effective technique which makes this surgical intervention a safe and [illegible]-free procedure.

Key words: enucleation – children.

While the enucleation of an eye from an adult patient usually gives no surgical difficulties, the same intervention in a child may be complicated in ways.

Psychologically the removal of the eye of a child is always a most unpleas[ant] ... The situation may lay a considerable stress on the part of the surgeon, and occasionally interfere with his skill. From the technical point of view the sm[all] ... all structures may cause troubles. The sclera may prove thin and the ... toothed enucleation forceps may lead to perforation with loss of intraocula[r] ... In case of a retinoblastoma this is not an acceptable complication.

While cutting the extraocular muscles rarely gives difficulties, the bl[ind] ... with a scissor in the retrobulbar tissue in an attempt to cut the optic nerve ... to a most stressing haemorrhage. To an ophthalmic surgeon even a ... haemorrhage is unusual and he is totally unfamiliar with the amount of ... haemorrhage in a small child. Compression is attempted but even ... operation is continued the haemorrhage recommences. After a certain ... time he may attempt to end the operation by several cuttings with the sc[issor] ... bleeding depth. He may realize that the lid aperture is too small to allow ...

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ioved and that this is the reason why the eye cannot be pulled out After a done canthotomy the eye is nervously removed while the bleeding continues rrect suturing of the conjunctiva is also impeded by the haemorrhage from eral unnecessary incisions in the retrobulbar tissue

n the above mentioned complications we find it worth while to report on a nple technique which we have now used for years on a fairly large number of n

Recommended technique

id speculum is inserted and the conjunctiva is incised along the corneal For this scissors are recommended as a thick and well defined conjunctival an be obtained when the subconjunctival tissue is included in the first cut

Curved pointed scissor is introduced along the globe in each of the four ints By opening the scissor the tissues are separated With a little experience ed only be done once and causes no haemorrhage

nuscle hook is placed behind each of the rectus muscles The conjunctiva is and separated from the muscle Now the muscle is cut *behind* the muscle leaving 1 2 mm of the muscle tendon on the globe

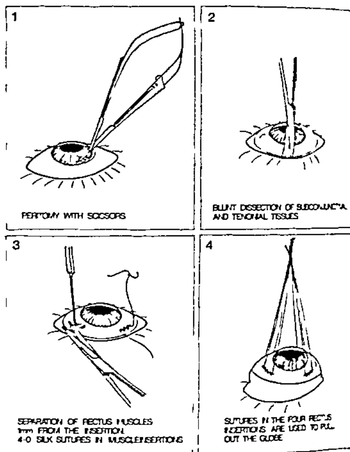
rough each of the four rectus insertions a double 4 0 silk suture is passed times A knot is made on the suture in the superior rectus for later fication

e four double sutures are twisted and grasped by a pean It is now easy to pull e forward The oblique muscles are caught by a muscle hook and cut

e eye speculum is removed and by pulling on the sutures the eye is gently d in front of the lid margins Now a strong curved scissor is introduced along iedial aspect of the eye The optic nerve is easily felt and can be cut at any ce from the globe Only the optic nerve is cut and therefore no or purely ial haemorrhage occurs

ie conjunctiva is sutured by an absorbable suture e g interrupted 5 0 vicryl

se of a retinoblastoma any implant may be considered erroneous as it may nt the early recognition of orbital recurrence If no malignancy is present any rred orbital implant can be used and the technique accordingly modified The ration shows the major steps in the operation (Figs 1-4)



Figs 1-4

Comments

The suggested technique of enucleation has been used in several operations ... been gradually developed over the years after some unpleasant experience ... the techniques found in many textbooks It may seem unnecessarily ... but it is our experience that the time spent at the beginning of the ... careful dissection and by placing the traction sutures is fully regained ... stages

Besides being a technical improvement it may be advantageous ... mechanically traumatic This might be preferable if tumour spread ... during mechanical manipulation on the eye This latter consequence ... understood if tumourcells are found in the anterior chamber but ... with no evident intraocular dissemination of the tumour

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RETINAL HAEMORRHAGES IN THE NEWBORN

BY

KJELL EGGE GAUTE LYNG and JAN MARTIN MALTAU

The pre ent study shows the frequency and se erity of retinal haemorrhages n 200 newborn of wh ch 100 were del ered spontaneousl 51 del ered b vacuum extractor and 49 by forceps The ncidence of retinal haemorrhages was h ghest n the vacuum group (50%) lowest in the forceps group (16%) wh le the spontaneously del vered children showed an ncidence of 41%
The ncidence of se ere ret nal haemorrhages was about f e times h gher n the vacuum group than in both forceps and control groups
The authors propose a quantitati e grad ng of the haemorrhages The purpose has been to obta n a bet er way of relating the haemorrhages to mode of del ery and probably also to rela e retinal haemorrhages to poss ble bra n damage

Key words ret nal haemorrhages newborn vacuum extract on forceps del very bra n njuries

al haemorrhages are commonly seen in the newborn during the f rst few days : They can vary cons derably from only a s ngle and small one to large and erous haemorrhages sometimes also apparently preretinal
ny stud es on this topic have been performed especially during the last 15 to ars The impetus for the present study was that during a short period in the nn of 1974 two newborn with extremely large and numerous haemorrhages observed They were both delivered by vacuum extraction This study was rtaken to see how the frequency and severity of retinal haemorrhages were enced by vacuum extraction and forceps del very in our hosp tal

ed May 4 19 9



Fig I
Retinal haemorrhages in newborn classified as grade I

Materials and Methods

From ultimo September 1974 to ultimo February 1976 ophthalmoscopy was [illegible] in 51 newborn delivered by vacuum extractor and 49 newborn deli[illegible] forceps consecutively In September 1975 100 consecutive spontaneously [illegible] vered newborn were examined in the same way and served as controls [illegible] examination took place during the first 72 hours of life

The newborn were delivered in the Department of Obstetrics and [illegible] Rikshospitalet, Oslo They all had a birth weight of more than [illegible] g [illegible] scopy was performed by the direct method using a diagnostic [illegible] Cyclopentholate chloride 1% eye drops (Cyclogyl®) was used as [illegible] examinations were all performed by the same ophthalmologist.

The retinal changes were classified in three grades (Fig 1–3)

Grade I was characterized by small mainly less than a quarter of the disc [illegible] and relatively few haemorrhages in one or both eyes

Grade II included medium large haemorrhages which were not [illegible] optic disc diameter in size or a combination of a few such haemorrhages [illegible] smaller ones in one or both eyes

Grade III included larger haemorrhages the diameter of which were [illegible] that of the optic disc, in one or both eyes Very often the haemorrhages [illegible] were extremely large several times the diameter of the optic disc and [illegible] also combined with smaller and/or larger apparently preretinal haemor[illegible]



Fig 2
Retinal haemorrhages in newborn classified as grade II

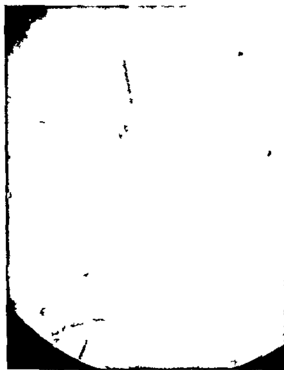


Fig 3
Retinal haemorrhages in newborn classified as grade III

According to studies of von Barsewisch (1979) it is reasonable to a[…] many of these so-called preretinal haemorrhages were not preretinal [...] situated beneath the internal limiting membrane.

Results

Table I shows that

a) the incidence of neonatal retinal haemorrhages was higher [...] delivered by vacuum extraction (50%) as compared with those deliver[...] neously (41%).

b) the incidence of retinal haemorrhages in newborn was double thos[...] spontaneously and about three times higher in those delivered by vacu[...] tion than by forceps.

c) the incidence of retinal changes classified as grade III was about [...] higher after vacuum extraction as compared with both forceps or s[...] delivery.

d) what also can be concluded from (c): the incidence of retinal haem[...] grade III was about equal in both spontaneous and forceps delivery.

Among children delivered by vacuum extractor 16 out of 17 with grade III had these large haemorrhages in both eyes while this was the c[...] of 7 in spontaneously delivered children. All 3 children with grade III d[...] forceps had these alterations in both eyes.

Concerning the haemorrhages of grade I among the spontaneous[...] children 13 out of 20 were affected in only one eye.

Table I
Frequency of retinal haemorrhages in newborn

	Grade III	Grade II	Grade I	hae[...]
Spontaneous delivery (n=100)	7%	14%	20%	
Vacuum extraction (n=51)	34%	8%	8%	
Forceps delivery (n=49)	6%	2%	8%	

Discussion

materıal in this study is relatively small However the observation that the ıency of large retinal haemorrhages is about five times higher after vacuum ıction as compared with forceps or spontaneous deliveries may in our opinion ıably be of considerable importance We also attach importance to the low ıence of retinal haemorrhages after forceps delivery

ıgh incidences of retinal haemorrhagges after vacuum extraction in relation to ıtaneous or forceps delivery have been previously noted by many authors hez Ibanez et al (1963) found retinal haemorrhages in 59 2% after vacuum action 33 6% after spontaneous delivery and 30 7% after forceps delivery uer Mayer (1965) found 50% after vacuum 20 5% after spontaneous delivery 19% after forceps The corresponding figures reported by Neuweiler & vudiwe (1967) were 72 4% 34 8% and 42 8% while Ehlers et al (1974) found : 27 5% and 38% respectively

he frequency of retinal haemorrhages after vacuum extraction is in this study greement with the studies mentioned above in the respect that the incidence in mode of delivery is considerably higher than after forceps or spontaneous very

s Sanchez Ibanez et al (1963) and Krauer Mayer (1965) we found the lowest dence of retinal haemorrhages in the forceps group while this was not the case ıe studies of Neuweiler & Onwudiwe (1967) and Ehlers et al (1974)

Iany authors give a description of the appearance and location of the hae rrhages (Brændstrup 1969 Ehlers et al 1974 and others) However the hitherto ıt comprehensive description of the different types of haemorrhages is probably ın by von Barsewisch (1979) in his monography on neonatal retinal haemorr ;es

o our knowledge very few attemps have been carried out to grade the morrhages quantitatively Krauer Mayer (1965) points out that after vacuum raction 15% severe retinal haemorrhages are seen against 2% by forceps and % in the control groups von Barsewisch (1979) has a quantitative subdivision in : groups from no retinal haemorrhages in group 1 to more than 20 haemorr ;es in group 5 with many visible sources of bleeding and a thrombosis like ture

Ve think however that it is better to give a quantitative grading related to the of the optic disc completed with a description

t is reasonable to consider retinal haemorrhages as a complication at birth pite the high incidence of haemorrhages also seen after apparently normal ntaneous deliveries The importance of these haemorrhages in the newborn is cure Studies of von Noorden & Khodadoust (1973) Lowes et al (1976) Richter

(1976) and others give no basis for an assumption of an increased freq... amblyopia or squint in patients with retinal haemorrhages at birth The... most difficult question is however whether there exists a clear connection... retinal haemorrhages in the newborn and brain damage for instance ... brain dysfunctions By grading the haemorrhages quantitatively as ... above we hope to give a contribution not only to a better way to rel... haemorrhages to mode of delivery but probably also to relate the haemorrh... possible brain damage In our opinion only long term studies of children ... *those with large and extensive retinal haemorrhages* may give us an answer ... important question

Acknowledgement

We are grateful to doctor T Flage for his assistance and help with fundus pho... venture which caused us a number of inconveniences

References

Brændstrup P (1969) Vitreous haemorrhages in the newborn *Acta ophthal (K...* 502–513

Ehlers N Krarup Jensen I & Brogård Hansen K (1974) Retinal haemorrhages ... newborn *Acta ophthal (Kbh)* 52 172–186

Krauer Mayer B (1965) Retinahaemorrhagien beim Neugeborenen Vergleichende ... suchungen nach Spontangeburten Vakuumextraktionen und Forceps ... 168–176

Lowes M Ehlers N & Krarup Jensen I (1976) Visual function after perinatal re... haemorrhage *Acta ophthal (Kbh)* 54 227–232

Neuweiler W & Onwudiwe E U (1967) Retinahamorrhagien beim Neugeborenen ... Geburtsverlauf *Klin Mbl Augenheilk* 149 483–490

Richter S (1976) Uber die Bedeutung von Netzhautblutungen Neugeborener ... *Grenzgebiete* 15 103–107

Sanchez Ibanez J M Belmonte Gonzales N & Navarro Martinez A (19... Hamorrhagien beim Neugeborener nach Vakuum Extraktion ...

von Barsewisch B (1979) *Perinatal Retinal Haemorrhages* Springer Verlag Berlin Heid... and New York

von Noorden G K & Khodadoust A (1973) Retinal haemorrhages in newborns and ... amblyopia *Arch Ophthal (Chicago)* 89 91–93

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CHILDHOOD BLINDNESS IN ICELAND

tudy of legally blind and partially seeing children in Iceland 1978

BY

SÆVAR HALLDÓRSSON and GUDMUNDUR BJÖRNSSON

In 1978 a study was made of legally blind (corrected visual acuity 6 60 or less) and partially seeing (CVA 6/18 to 6/60) children under 15 years of age in Iceland A total of 43 children were found of whom 23 were legally blind and ?0 partially seeing The prevalence rates expressed as the number per 100 000 children of similar age 36 4 for legal blindness and 31 6 for partial sight

In all 43 children the visual loss was attributable to heritable congenital or developmental defects The most common causes of visual loss were optic nerve atrophy and cataracts Other causes are listed and discussed No cases of aquired visual loss were found In addition to visual loss other congenital birth defects were found in 24 of the children CNS affection was found in 20 of the children and of these 15 were mentally retarded

Key words blindness – legal blindness – partial sight – congenital blindness – childhood blindness – hereditary blindness

following *study was made in 1978 to determine the prevalence and causes of* ness and partial sight in children in Iceland While blind children have been ed twice before in Iceland no study has previously been made of partially g children (Sveinsson 1944 Bjornsson 1955) Prevalence rates are presented ll as causes and a few cases histories are presented briefly

ved August ?7 1979

Materials and Methods

Information as to the number of blind and partially seeing children was [illegible] by polling all practicing ophthalmologists and social workers at the S[illegible] Blind Records at the School for the Blind were reviewed and children [illegible] the school were examined by the authors Visual acuity figures and causes [illegible] loss are in all cases based on an ophthalmologist's examination. [illegible] children including all of those with multiple defects were also exam[illegible] pediatrician Nineteen of the children had been admitted at least [illegible] St Joseph's Hospital and in these cases their records were reviewed

For this study the WHO difinition of blindness was used (corrected v[illegible] of 6/60 or less in the better eye or a visual field of 20 or less in the be[illegible] Partial sight is defined as corrected visual acuity from 6/18 to 6/60 in the be[illegible]

Results

A total of 43 blind and partially seeing children under 15 years of age we[illegible] Of these 43 children 23 were blind and 20 were partially seeing T[illegible] prevalence rates (Table I) for blindness and partial sight in children unde[illegible] of age were 36 4 and 31 6 per 100 000 children of comparable age re[illegible] Distribution of the children by corrected visual acuity is presented in Table [illegible]

Table III shows distribution of the children by site and/or type of eye [illegible] and Table IV shows distribution by etiology In all cases the visual [illegible]

Table I
Prevalence rates of legal blindness and partial sight by age

	Population Dec 1 1977	Legal blindness		Partial sight	
		Number	Rate 100 000 population	Number	Rate 100 000 population
0–4	20 142	4	19 8	4	[illegible]
5–9	20 531	11	53 [illegible]	7	[illegible]
10–14	22 493	8	3[illegible] 5	9	[illegible]
	63 166	23	3[illegible]	[illegible]0	31[illegible]

Table II

Distribution of 43 legally blind or partially seeing children by corrected visual acuity and sex.

Corrected visual acuity	M	F	Total
No light perception	2	1	3
Light perception to finger counting at 1 m	2		2
1/60 to 6 60 Snellen	11	7	18
6/18 to 6/36 Snellen	16	4	20
Total	31	12	43

Table III

Distribution of 43 legally blind or partially seeing children by site and/or type of affection and by age

Site/type of affection	Age			
	1–4	5–9	10 14	Total
Eyeball in General				
Glaucoma		1		1
Anophthalmos and microphthalmos	2	1	2	5
Albinism		6	1	7
Cornea			1	1
Lens				
Cataracts	2	5	4	11
Lens subluxation		1		1
Optic nerve and pathway				
Optic nerve atrophy	3	4	5	12
Nystagmus	1		3	4
Retina				
Macular degeneration			1	1
Total	8	18	17	43

Table II

Distribution of 43 legally blind or partially seeing children by etiology and visual acuity

	Partial sight	Legal blindness	Total
A Hereditary – Congenital			
Albinism – nystagmus		7	
Zonular cataracts	1		1
Down syndrome (Trisomy 21) – cataracts		1	1
Friedreich's ataxia optic atrophy		1	1
Congenital glaucoma	1		1
Microphthalmos anophthalmos		2	2
Monochromatismus (nystagmus)	1		1
Neurofibromatosis optic atrophy		1	1
Smith Lemli-Opitz syndrome lens subluxation		1	1
Spielmeyer Vogt's syndrome optic atrophy		1	1
B Other congenital			
Anophthalmos		1	1
Cataracts	7	2	9
Hydrocephalus optic atrophy	2		2
Microphthalmos		2	2
Nystagmus	3		3
Corneal opacity	1		1
Optic atrophy	3	4	7
Macular degeneration	1		1
Total	20	23	43

attributable to hereditary congenital or developmental defects The fe common causes were optic nerve atrophy cataracts albinism and m anophthalmos and together they accounted for 35 (81 3%) of the cases

The most common cause of visual loss was optic nerve atrophy which accoun (27 9%) of the cases Of the 12 7 were blind and 5 partially seeing Among the cases born 1976 who had localized cerebral atrophy but with the exception of visual otherwise normal A girl born 1968 has Friedreich's ataxia and her older sister als

›ease Optic nerve atrophy began at the age of 4 years in both and they are now blind
ıd severely ataxic A boy born 1968 had neurofibromatosis like his mother and at
of 3 optic nerve atrophy was found and attributable to a tumor in the chiasma The
as inoperable but responded well to radiation therapy which did not further impair

⁻ acts accounted for 11 (25 5%) of the cases Of these 8 are partially seeing and 3 are
ᴱ–)f the 9 children with cataracts in category B Table IV 9 are blind and 7 partially
All 9 have been operated on for cataracts Of the 9 2 have nystagmus and 1 has a
ıtal heart defect

ıism accounted for 7 (16 2%) of the cases All were classified as blind since the
ed visual acuity was 6 60 or less They all functioned as well as the partially seeing
n and those who were of school age were enrolled in public shools All have nystagmus
)st have astigmatismus Five have strabismus and of these four have been operated on
the seven are sisters and they have an older albino brother not included in this study
o- and anophthalmos accounted for 5 (11 6%) of the cases All five were blind A boy
967 has microphthalmos cleft palate and severe mental retardation A boy born
ıas anophthalmos a congenital heart defect (Fallot s tetralogy) and mental retardation
born 1977 has microphthalmos microcephalus and mental retardation The family
in all 3 cases was negative A girl born 1967 had one eye removed at age 2 weeks
‹e of a suspected neoplasm No neoplasm was found and she has microphthalmos of
ıer eye Her brother born 1971 has microphthalmos of one eye and leucoma of the
ı in the other eye He also has a congenital heart defect and hare lip The mother has a
nital defect of the lacrimal apparatus

e 43 children 24 (55 8%) have other defects in addition to visual loss Five
hearing loss and three have congenital heart defects Twenty have some
tion of the CNS fifteen of these being mentally retarded Thirteen have
ismus and seven of these have been operated on
none of the 43 cases were the parents first cousins

Discussion

study of blindness made in 1940 K Sveinsson found 7 blind children under
ıge of 20 (Sveinsson 1944) During the National Census of 1950 9 blind
ren under 20 years of age were found (prevalence rate 15 9 per 100 000
ren of comparable age) (Bjornsson 1955) We found 23 blind children under
ars of age which translates to a prevalence rate of 36 4 per 100 000 We found
ᶠartially seeing children under 15 years of age for a prevalence rate of 31 6 per
000 No previous studies of partial sight have been made in Iceland
the present study the cause of visual loss was in all cases attributable to
ditary congenital or developmental defects It is known that at least 22 blind
ˌlren were born in Iceland between 1941 and 1960 Nineteen of these had

congenital cataracts and of these 10 had congenital rubella. Two ... atrophy and one had bilateral retinoblastoma (Sigurjonsson 19...). ... found no cases of blindness or partial sight attributable to congenital ... surprising considering that Iceland had a rubella epidemic 19... Following the 1963 epidemic, 37 children with congenital rubella ... have been examined by the authors. While 57% of the children ... retinopathy none had cataracts or significant visual loss (Baldursson et al.) Following the 1972-73 epidemic, a boy was born with congenital rubella ... blind with bilateral cataracts but died during his second year of ... disease. Another congenital rubella child born 1974 has a unilateral ... normal vision in the other eye.

In a study from the United States in 1969 Hatfield found a prevalence ... blindness 39.3 per 100 000 among shool age children (Hatfield 19...). ... parable age group in our study had a prevalence rate of 44.1 per 100 000 ... visual loss in the American study were intrauterine infections 9.8% ... poisonings (including retrolental fibroplasia) 7.9% tumours 5.7% ... 1.4% prenatal influences 49.9% and unknown 35.6% (Hatfield 19...) ... study hereditary congenital and developmental defects accounted ... loss in all cases. In the American study they accounted for 49.9% of the ... case of RLF has ever been found in Iceland whereas an American ... showed that RLF accounted for 8.4% of blindness in children 5-9 years, 14.8% 10-14 years of age and 40.7% 15-19 years of age.

It may also be mentioned that during the present study several children ... found who had unilateral visual loss. Causes included congenital rubella, toxoplasmosis, accidents, keratitis, neoplasms, Sturge-Weber's syndrome, Goldenhar's syndrome.

References

Baldursson G, Bjarnason O, Halldorsson S, Juliusdottir F & Kjeld M ... rubella in Iceland 1963-1964. Scand Audiol 1, 3-10.

Bjornsson G (19...) Prevalence and causes of blindness in Iceland. ... 202-208.

Hatfield E. M. (1975) Why are they blind. Sight Saving Rev. 45, 2-... ...

Sigurjonsson J. (1962) Rubella and congenital cataract blindness. Med. J. ...

Sveinsson K. (1944) Blindness in Iceland. Health and Life. Vol 1-2.

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ANGIOTENSIN CONVERTING ENZYME IN UVEITIS AND SARCOIDOSIS

BY

FRODE K RØMER PETER SCHMIDT and HANNE GEDAY

Serum angiotensin-converting enzyme (SACE) was studied in a group of 29 sarcoidosis patients (among whom five had uveitis) and in 22 patients with non sarcoid uveitis

SACE was normal in all non sarcoid patients and elevated in 69 per cent of the patients with sarcoidosis

Thus an elevated SACE is closely linked to sarcoidosis and may be a valuable tool in evaluating patients with uveitis in search of a sarcoid origin

Key words angiotensin – converting enzyme – uveitis – sarcoidosis

oximately half of the patients with uveitis the etiology is unknown (James et 5 ab Kauffman 1966 Perkins 1976) Uveitis occurs as a complication in a r of infectious disorders and in diseases in which immunological mechanisms own to play a decisive part e g rheumatoid arthritis ankylosing spondylitis coidosis

irope about seven per cent of the cases of uveitis are caused by sarcoidosis in lisease ocular involvement occurs in 15 20 per cent of the patients submitted halmological examination (James et al 1976b Rømer et al 1973)

oid uveitis can be acute or chronic Frequently affected are females in the age 20-50 years (James et al 1976b) The ocular lesion is most often a bilateral clitis In acute sarcoid uveitis there is turbidity of the aqueous with few cells ie keratic precipitates In the chronic iridocyclitis nodules on the iris and i fat keratic precipitates are formed The posterior uveitis consists of vascular

d March 9 1979

sheathing choroidal nodules (waxy exudates or chorioretinitis [illegible] bougie") (Bruntse 1958) haemorrhages and papilloedema

In recent years serum angiotensin-converting enzyme (kininase II) [illegible] been found to be elevated in sarcoidosis (Lieberman 1975)

The present paper is part of a study on SACE in sarcoidosis [illegible] granulomatous diseases The purpose was to examine SACE in [illegible] sarcoidosis patients with or without uveitis compared with patients [illegible] sarcoid uveitis

Material

A survey of the patients is given in Table I The series consisted of

1) Twenty two patients with non-sarcoid uveitis male female ratio [illegible] years The patients were referred to the Eye Department during a [illegible] period in 1977 78 The patients with uveitis underwent a standard [illegible] *programme including chest X ray and clinical and* laboratory [illegible] underlying infectious or rheumatic diseases

2) Twenty nine patients with active sarcoidosis male female ratio [illegible] years Sarcoidosis was in most cases diagnosed at the Department of [illegible] the Chest Clinic during 1977 78

The sarcoidosis patients were staged according to chest X ray Stage I [illegible] paratracheal adenopathy Stage II hilar or paratracheal lymphadenopathy [illegible] *pulmonary involvement* and *Stage III* pulmonary involvement alone [illegible] detectable lymphadenopathy In 16 out of 29 sarcoidosis patients [illegible] granulomas were demonstrated In 13 patients the diagnosis was made [illegible]

Table I

Survey of the patients included in the study

	No of patients		No of patients
Non-sarcoid uveitis	22	uveitis total	[illegible]
Sarcoid uveitis	5	sarcoidosis total	[illegible]
Sarcoidosis without uveitis	24		
	51		

ical and roentgenological features and other diseases resembling sarcoidosis rculosis lymphomas Yersinosis etc) were ruled out

g all 51 patients eight received systemic corticosteroids at the time of the first sampling Ophthalmic examination included external and slit lamp examina phthalmoscopy and testing of the vision

Methods

i angiotensin converting enzyme (SACE)

patients SACE was determined in sarcoidosis patients simultaneously (+/− ionths) with the ophthalmological examination in patients with nonsarcoid regularly at their first visit at the ophthalmological department and in most repeated after 2-4 weeks The SACE analysis was performed using the od of Cushman & Cheung (1971) modified by Lieberman (1975) The natural rate Angiotensin I was replaced by a synthetic substrate analogue the tripep uppuryl histidyl leucine (Bio Science Products AG Reusbuhl Switzerland) which SACE liberates hippuric acid The amount of liberated hippuric acid e measured by spectrophotometry at 228 nm and is a measure of the enzyme ty SACE is expressed in units which are equivalent with nanomol hippuric ormed per min/ml A 60 min assay at 37 C at ph 8 3 was used

od was obtained by venipuncture and serum was stored at −20°C until zed After 12 months storage no loss of enzyme activity was found

rmal values of SACE was 12 0 36 8 units (mean ± 2 SD in 116 healthy persons 18-65 years)

tics

rence in mean values was tested with a Student s *t* test Pair-differences were d with a Wilcoxon test significance level was five per cent

Results

sarcoid uveitis

e uveitis with an abrupt onset and a duration of weeks or months was found in atients (59%) while 9 patients had chronic uveitis with an insidious onset and a tion of months up to years with several recurrent attacks during the years eding admission

nterior uveitis (iritis iridocyclitis) was found in 10 patients (46%) posterior tis (retinochoroidal affection and/or vitreous blurring without affection of the

Table II

Serum angiotensin-converting enzyme (SACE) in patients with non sarcoid uveitis

	No of patients	SACE units (1?0 3?)	
		Mean ± SD	Range
Total	22	23 6±6 8	11 35
With associated disease	5	21 5±8 4	11 335
Without associated disease	17	26 6±7 9	11 8 3?
Anterior uveitis	10	?1 8±6 9	11 7 3 5
Posterior uveitis	8	24 8±5 8	11 8 335
Panuveitis	4	2? 7±6 0	19 4 33
Acute uveitis	13	22 8±7 3	11 7 335
Chronic uveitis	9	?4 8±5 3	11 9 3?

anterior segment) was found in 8 patients (36%) and panuveitis (all affected) in 4 patients (18%)

Associated disorders were found in five patients (23%) including Reiter's ankylosing spondylitis unclassified connective tissue disease with pr... glomerulonephritis rheumatoid arthritis and one case of paran... protracted course

As shown in Table II SACE was entirely normal in all patients No ... difference in SACE was found due to presence or not of associated disorders to clinical subgroups of uveitis

Patients with sarcoidosis

SACE was significantly raised compared with non sarcoid uveitis and controls ($P < 0\ 001$) in 62% (Table III)

No difference in SACE was found according to chest X ray stage or d... disease although the figures in Table III show a trend toward higher ... and a higher proportion with a chronic course (>2 years)

There was no significant difference in frequency of elevation or in ... SACE between patients with sarcoidosis in whom epitheloid granulomas ... demonstrated (69% SACE 44 4 ± 16 1 (1 SD)) and those where a biopsy ... taken (54% SACE 41 2 ± 21 1)

In two out of five patients with sarcoid uveitis SACE was elevated (41 1 ... 49 1 u respectively) The three other patients were all under prednisone ...

The five patients with sarcoid uveitis were 4 females (age 29-56) and ... (age 43) All were bilateraly affected and the uveitis was chronic in all ...

Table III

Serum angiotensin-converting enzyme (SACE) in 29 patients with sarcoidosis

	No of patients	SACE, units (19 0–36 8)		No. of patients with elevated SACE	No of patients with uveitis
		Mean±SD	Range		
d	29	49 9±18 2	21 8–102 1	18 (62%)	5 (17%)
t X ray stage					
	11	38 7±14 8	21 8– 65 2	6 (55%)	2 (18%)
	17	46 8±19 9	23 0–109 1	12 (71%)	2 (12%)
I	1	24 0	24 0	0	1
ation < 2 years	20	40 7±18 0	21 8–109 1	11 (55%)	1 (5%)
ation > 2 years	9	47 9±18 7	24 4– 84 8	7 (78%)	4 (44%)

anterior uveitis with the findings previously mentioned but nodules on iris not seen One patient had panuveitis with characteristic candle-wax spots in etina One of the female patients with anterior uveitis had papilloedema in the eye

during treatment

tal of four patients with sarcoidosis (three with and one without uveitis) were r prednisone treatment at the time of the sampling of blood for analysis All had normal SACE

ten non sarcoid uveitis patients SACE was measured two or four weeks after initiation of prednisone theraphy 40-80 mg daily In two patients a decline of E on 20-30% was observed but in the group as a whole no significant decline found

Discussion

recent years serum angiotensin-converting enzyme has been found to be ated in sarcoidosis (Lieberman 1975) but not in tuberculosis (Lieberman 1975 ner 1979) or malignant lymphomas (Rømer 1979) It was the main purpose of study to investigate the specificity of elevated SACE in a group of patients with ical and etiological connexion with sarcoidosis i.e. uveitis In this paper we have onstrated that non sarcoid uveitis is not followed by elevation of SACE reas mean SACE in 29 sarcoidosis patients was significantly raised in 62% of patients giving a diagnostic specificity (the predictive value of a positive test)

Table II

Serum angiotensin-converting enzyme (SACE) in 22 patients with non-sarcoid uveitis

	No of patients	SACE, units ([illegible])	
		Mean ± SD	Range
Total	22	23.6±6.8	11.7–35
With associated disease	5	21.5±8.4	11–33.3
Without associated disease	17	26.6±7.9	14.8–35
Anterior uveitis	10	21.8±6.9	11.7–[illegible]
Posterior uveitis	8	24.8±5.8	14.8–33.3
Panuveitis	4	25.7±6.0	19.4–35
Acute uveitis	13	22.8±7.3	11.7–33.3
Chronic uveitis	9	24.8±5.3	14.8–35

anterior segment) was found in 8 patients (36%) and panuveitis (all affected) in 4 patients (18%).

Associated disorders were found in five patients (23%) including Reiter, ankylosing spondylitis, unclassified connective tissue disease with pr glomerulonephritis, rheumatoid arthritis and one case of panu[illegible] protracted course.

As shown in Table II SACE was entirely normal in all patients. No [illegible] difference in SACE was found due to presence or not of associated disorder to clinical subgroups of uveitis.

Patients with sarcoidosis

SACE was significantly raised compared with non-sarcoid uveitis and controls ($P < 0.001$) in 62% (Table III).

No difference in SACE was found according to chest X-ray stage or d[illegible] disease although the figures in Table III show a trend toward higher [illegible] and a higher proportion with a chronic course (>2 years).

There was no significant difference in frequency of elevation or in mea[illegible] SACE between patients with sarcoidosis in whom epitheloid granuloma[illegible] demonstrated (69%, SACE 44.4 ± 16.1 (1 SD)) and those where a biopsy [illegible] taken (54%, SACE 41.2 ± 21.1).

In two out of five patients with sarcoid uveitis SACE was elevated ([illegible] 49.1 u respectively). The three other patients were all under pred[illegible] [illegible]

The five patients with sarcoid uveitis were 4 females (age 29–59) and on[illegible] (age 43). All were bilaterally affected and the uveitis was chronic in all [illegible]

rman J (1975) Elevation of serum angiotensin-converting enzyme (ACE) level in coidosis *Amer J Med 59* 365–372
ns F S (1976) Epidemiology of uveitis *Trans. ophthal. Soc U.K. 96* 105–107
r F K (1979) Angiotensin-converting enzyme in sarcoidosis *Acta med scand 206* –30
r F K Paulsen S Antonius V Nielsen J L & Hommelgaard P (1973) Sarcoidosis in a nish "Amt A retrospective epidemiological study of sarcoidosis in Ringkøbing Amt m 1960–1969 *Danish med Bull 20* 112–120
rstein E Friedland J Lyons H A & Godrin A (1976) Markedly elevated angiotensin nverting enzyme in lymph nodes containing non necrotizing granulomas in sarcoidosis *oc nat Acad Sci* (Wash) *73* 2137–2141
r R L (1976) angiotensin-converting enzyme and the regulation of vasoactive peptides *n Rev Biochem 45* 73–94

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of $\frac{18}{18+0} = 1.0$ and a diagnostic sensitivity (the predictive value of a te

of $\frac{22}{22+11} = 0.67$ (sarcoidosis vs non sarcoid uveitis). Thus normal
not rule out sarcoidosis but elevated SACE points strongly towards sar
series of sarcoidosis patients was too small for splitting up into subgroup
a trend toward higher frequency of elevated SACE was found in pa
chronic disease (duration > 2 years). This trend has been confirmed
series of 85 patients (Rømer 1979).

Angiotensin-converting enzyme (ACE) converts angiotensin I into th
angiotensin II (Stoffer 1976). It is normally generated in the endo
mainly in the lungs. The reason for the elevation of SACE in sarcoidos
but the finding of a high ACE activity in sarcoid lymph nodes
ACE formation in epitheloid-cells (Silverstein et al. 1976) and pro
increased synthesis in these monocyte macrophage derived cells.

In spite of the important role of ACE in formation of angiotensin I
correlation between SACE level and blood pressure. The enzyme
bradykinin (kininase II) and it may be that the increased level in sarco
a change of the kinin metabolism during a low grade granulomatous

Conclusion

Based on our results we conclude that elevated SACE is a valuable dia
sarcoidosis and in evaluating uveitis an elevated SACE strongly indica
origin.

Acknowledgment

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References

Bruntse F. (1958) Ocular Sarcoidosis. *Danish med. Bull.* 5, 217–21
Cushman D. W. & Cheung H. S. (1971) Spectrophotometric assay and proper angiotensin-converting enzyme of rabbit lung. *Biochem. Pharm.* 20, 1637–16
James D. G., Friedman A. J. & Graham E. (1976a) Uveitis. *Trans. ophth. S.* 108–112
James D. G., Neville E. & Langley D. A. (1976b) Ocular sarcoidosis. *Trans. oph.* 96, 133–139
Kauffman H. E. (1964) The Uvea. *Arch. Ophthal. (Chica.)* 75, 407–431

eral cell loss can be assessed retrospectively by using the contralateral eye as a
ol

ently a low endothelial cell density has been reported in some patients with
cyclitis (Setala 1979)

Subjects and Methods

en patients were included in the study They comprised all patients who had been ed to the eye clinic for the past one and a half years with one to several attacks of acute ral uveitis Mean age was 40 2 years range 23-69 years With the exception of two s who showed a weak seroreaction for toxoplasmosis no underlying etiology to the was found in any of the patients In three patients the anterior uveitis coexisted with a ior uveitis During admission all patients were noted to have increased thickness or oedema of the cornea and precipitates were found on the posterior aspect of the Patients were not classified according to the type of the precipitates At the time of rge one patient had elevated intraocular pressure on the affected side while the nder of the patients had normal pressures (appl)

shortest time period between discharge from the hospital and the present examination ree months (range 3-18 months) With the exception of three patients who showed a

Table I

ensity and central corneal thickness (CCT) in 13 patients with previous unilateral acute anterior uveitis

ent No	Age	Cell density (cells mm²)		CCT (mm)	
		Normal eye	Affected eye	Normal eye	Affected eye
1	66	2825	2682	0 510	0 515
2	33	2834	2666	0 520	0 520
3	23	3113	3039	0 520	0 420*)
4	41	2908	2945	0 505	0 495
5	20	3486	3328	0 520	0 545*)
6	61	2703	2759	0 490	0 500
7	35	3146	3281	0 525	0 535
8	49	2778	2330	0 520	0.540)
9	25	2796	2889	0 525	0.530
10	35	3281	2573	0 510	0 540**)
11	69	2796	2852	0 560	0 560
12	42	2983	2306	0 520	0 515
13	23	2950	3202	0 505	0 515

healed corneal ulcer on that side
faint aqueous flare on that side

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CHANGES IN THE CORNEAL ENDOTHELIUM AFTER ACUTE ANTERIOR UVEITIS AS SEEN WITH THE SPECULAR MICROSCOPE

BY

THOMAS OLSEN

In order to investigate whether inflammation of the anterior uveal tract is accompanied by a loss of endothelial cells 13 patients with previous unilateral attacks of anterior uveitis were photographed with the non-contact specular microscope All patients had shown an increased thickness or frank oedema of the cornea during the acute phase of the inflammation As compared to the healthy eye only two patients (15%) showed endothelial cell densities on the affected side which were lower than was to be expected from the normal difference between counts from left and right eye in a control population of subjects The two patients with detectable cell loss also showed defects in the specular reflex the significance of which is discussed

Key words cornea – endothelium – non-contact – specular microscopy – uveitis

Inflammation of the uveal tract is well known to have concomitant effects on the cornea In acute anterior uveitis the corneal thickness increases (Mishima & Polak 1969 Capella & Waltman 1971) and following the acute attack changes in the specular reflex of the endothelium have been described (Vogt 1930)

The increase in corneal thickness associated with the acute inflammation suggests that the barrier function of the endothelium is temporarily disturbed and raises the question of whether this is due to a loss of cells

Due to the limited proliferative power of the adult human endothelium (Kaufman et al 1966 Stocker 1971) and the high concordance between cell densities from right and left eyes in normal eyes (Sturrock et al 1978 Olsen 1979 1980)

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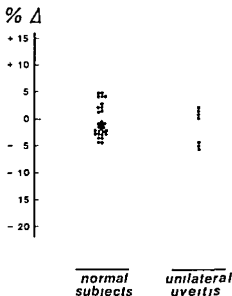


Fig 1

...ive inter-eye difference in cell counts in 13 patients with previous unilateral anterior ...rdinate = $\frac{\text{affected eye} - \text{unaffected eye}}{\text{unaffected eye}} \times 100\%$) as compared to the relative difference in 36 normal subjects ... = $\frac{\text{x eye} - \text{contralateral eye}}{\text{contralateral eye}} \times 100\%$ x denotes randomly chosen right or left eye

...) they were seen as old large sharply demarcated precipitates Besides the ...ial occurrence of scattered physiological guttae none of the other patients ... this type of change in the specular reflex

...al corneal thickness (CCT) was measured in both eyes of 47 normal ... 95% confidence limits for the normal difference between thickness of ...d left eye (CCT left eye – CCT right eye) was –0 013 mm and +0 016 mm ...vely In practical terms this means that a difference of 0 02 mm or more is ...abnormal From Table I it is seen that three of the patients (Nos 5 8 and 10) ... a CCT on the affected side which differed more than normal from the ...ateral side These patients also showed a faint aqueous flare on the affected ... two of these patients a detectable cell loss had been found

ıpatıents wıth detectable cell loss ın the present study also showed numerous ın the endothelıal reflex One of these patıents also had elevated ıntraocular re so that an effect of thıs on the appearance of the endothelıum cannot be ed (Setala & Vannas 1978) The other patıent dıd not show thıs complıcatıon e observed defects were clearly dıfferent from ordınary guttae Vogt (1930) ɔed excrescences on the posterıor aspect of cornea after ınflammatıon as ırregular than ordınary guttae The defects ın the endothelıal reflex seen ın resent study were however large and almost cırcular gıvıng an ırregular only when they were confluent. In contrast to senıle physıologıcal guttae llular outlıne of the endothelıum lınıng the posterıor aspect of these cences could not readıly be seen by alterıng the angle of ıllumınatıon or ng depth The ımpressıon was that of a hyalıne materıal deposıted between ıembrane of Descemet and the endothelıal layer In experımental uveıtıs ımatory cells have been shown to enter thıs subendothelıal space (Inomata & er 1970) It ıs temptıng to speculate that ıf the defects ın the specular reflex n the present study constıtute remnants of precıpıtates formed ın the acute of the ınflammatıon they have gaıned access to the subendothelıal space gh a breakdown of the endothelıal layer Persıstıng precıpıtates seen as ts ın the specular reflex may thus be ındıcatıve of endothelıal cell loss

e two patıents showıng a decrease ın the cell densıty on the affected sıde also thıcker cornea on that sıde together wıth a faınt aqueous flare It ıs dıffıcult to e thıs mınor ıncrease ın thıckness to a relatıve decompensatıon of the thelıum as a result of damage ın the acute phase or due to the stıll present nmatıon ın the eye The one patıent showıng an ıncrease ın thıckness wıthout a ase ın cell densıty suggests the latter possıbılıty

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References

la J A & Waltman S R. (1971) Corneal thıckness durıng corneal homograft rejectıon uveıtıs ın rabbıts *Amer J Ophthal.* 72 383–389

s N & Sperlıng S (1977) A technıcal ımprovement of the Haag Streıt pachometer *Acta thal (Kbh)* 55 333–336

ata H & Smelser G K (1970) Fine structural alteratıons of corneal endothelıum durıng erımental uveıtıs *Invest. Ophthal.* 9 272–285



Fig 2

...pic appearance of two corneal endothelia which showed ... following acute anterior uveitis Top guttae-like ... year-old male with recurrent attacks of iridocyclitis ... lesions in the endothelial reflex of 35-year-old female ... attacks of panuveitis Bar = 100μm

Discussion

Since Leber's time (1873) a destruction of the endothelium has been ... abnormal hydration of the cornea The specular microscope enables the ... to be quantitated if it has implied a loss of endothelial cells

The patients included in this study have all had increased thickness ... oedema of the cornea during the acute phase of their anterior uveitis ... patients (15%) showed a significant cell loss on the affected side In these patients at least part of the abnormal hydration of the cornea noted ... acute phase of the inflammation can thus be ascribed to a destruction ... endothelial cell layer In the great majority of the patients however ... destruction could be detected Therefore in these patients other factors ... sought for the increased hydration of the cornea Whatever the nature of ... factors may be the possibility remains that they may act by increasing ... permeability of the endothelium without causing actual cell death.

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THE ENDOTHELIAL CELL DAMAGE IN
CUTE GLAUCOMA ON THE CORNEAL THICKNESS RESPONSE
TO INTRAOCULAR PRESSURE

BY

THOMAS OLSEN

In order to asses a possible damage to the corneal endothelium during pressure induced abnormal hydration of the cornea 23 patients with a previous attack of unilateral acute glaucoma were photographed with the specular pe As compared to the healthy side the endothelium of the affected wed a mean decrease in cell density of 23 1% range −4 8 to 68% 1) In retrospect this cell loss was found to correlate significantly to the in corneal thickness measured during the acute attack on first day of At present examination mean central corneal thickness was identical ected and unaffected eye A large variation was however found in cular pressure of the previously attacked eye If the subject inter-eye in intraocular pressure was related to the inter-eye difference in ckness a significant negative correlation appeared
ded that the intraocular pressure has a dual effect on the corneal if the endothelium is intact the intraocular pressure decreases kness whereas an increase is seen only if the endothelium is acutely

rnea – endothelium – acute glaucoma – corneal thickness –
ssure – specular microscope

of the cornea may occur as epithelial and/or stromal oedema known clinical feature of increased intraocular pressure In en explained to occur when the interstitial fluid pressure of sitive (Ytteborg & Dohlman 1965a) and may as such occur

raocular pressure on the total corneal hydration of which

Kaufman H E Capella J A & Robbins J E (1966) The human corneal endo...
J Ophthal 61 835–841
Leber T (1873) Studien uber den Flussigkeitswechsel im Auge Albrecht v Graefes ...
Ophthal 19 87–185
Mishima S (1968) Corneal thickness Surv Ophthal 13 57–96
Olsen T (1979) Non-contact specular microscopy of human corneal endothe... ophthal (Kbh) 986–998
Polack F M (1965) The effect of ocular inflammation on corneal grafts Amer J ... 259–269
Setala K (1979) Corneal endothelial cell density in iridocyclitis Acta ophthal ... 277–286
Setala K & Vannas A (1978) Endothelial cells in the glaucomato-cyclitic crisis ... 36 218–224
Stocker F (1971) The endothelium of the cornea and its clinical implications ... Springfield Charles C Thomas Ill
Sturrock G D Sherrard E S & Rice N S C (1978) Specular microscopy of the ... endothelium Brit J Ophthal 62 809–814
Vogt A (1930) Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden ... 201 Verlag von Julius Springer Berlin

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: shortest time period between onset of attack and present examination was one month 13 months One patient with haemorrhagic glaucoma was receiving antiglaucomatous nent on the affected eye while the rest of the patients either received the same medical nent to both eyes (three patients) or were without medication at all

e control group comprised 39 subjects in the age range 50 97 years (mean 72 years) with story of eye disease or trauma other than senile lens opacities Some of these subjects been included in the normal series previously reported by Olsen (1979)

e central endothelium of both eyes of patients and normal subjects were photographed entral endothelial cell densities estimated as described earlier (Olsen 1979) From the ol group a normal relative inter-eye variation in cell density was constructed by omly choosing right or left eye as reference for the observed difference in cell counts By this the small systematical right left difference observed in normal eyes (Olsen 1979) is cted In the acute glaucoma group the difference in cell counts observed between the ted and the unaffected eye was expressed as relative to the unaffected eye

order to ascertain a possible damage to the endothelium during glaucoma-operation 7 eyes were photographed before and after (range 3 5 months) a trabeculertomy or ctomy in that eye

ntral corneal thickness was measured using a modified Haag Streit pachometer (Ehlers erling 1977) Intraocular pressure was measured using a Goldmann applanation meter attached to the slit lamp

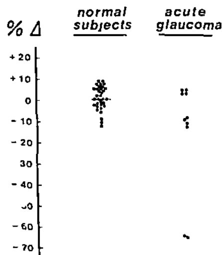


Fig 1

inter-eye differences in cell counts in 93 patients with previous attack of acute glaucoma ne side

$$\text{inate} = \frac{\text{affected eye} - \text{unaffected eye}}{\text{unaffected eye}} \times 100\%$$) as compared to the relative inter-eye rence in a group of normal subjects

$$\text{linate} = \frac{\text{x eye} - \text{contralateral eye}}{\text{contralateral eye}} \times 100\%$$ x denotes randomly chosen right or left eye)

stromal hydration constitutes a large part is however a confusing and [illegible] subject in ophthalmological literature Does the intraocular pressure [illegible] the stroma or does it oppose the swelling tendency of the cornea?

The clinical index of total corneal hydration is the corneal thickness [illegible] 1968) In clinical studies both increased (Ytteborg & Dohlman 1965a Pe[illegible] al 1976) and decreased (Sbordone 1953 Olson & Kaufman 19[illegible]) corne[illegible] have been observed with increased intraocular pressure An increase [illegible] thickness following a decrease in intraocular pressure has also been [illegible] (Ehlers & Riise 1967 Ehlers 1970) In vitro experiments have shown the [illegible] pressure to increase (Harris et al 1956 Maurice & Hoefle 1973) and [illegible] (Mayes & Hodson 1978) corneal hydration in experiments where the end[illegible] is claimed to be intact

The above mentioned studies have largely dealt with intraocular pressure [illegible] the physiological range and elevated pressures as they are encou[illegible] angle and secondary glaucomas In severe cases of increased intraocul[illegible] e g in acute glaucoma there is general agreement that in addition to the [illegible] oedema a stromal oedema may develop (see Fuenne 1960 Chandler 1965)

Since Leber's time (1873) the corneal endothelium has been known to b[illegible] factor for the water permeability of the cornea A study on the state of the endothelium during pressure induced abnormal hydration of the cornea [illegible] seemed indicated

Subjects and Methods

Twenty three patients in the age range 50-81 years with a mean of 69 years [illegible] the study They comprised all patients who had been admitted to the eye [illegible] two years with one unilateral attack of acute glaucoma Nineteen patients (15 [illegible] men) had suffered from acute angle closure glaucoma while 4 patients (3 [illegible]) had acute haemorrhagic glaucoma Patients with any other history of disease [illegible] either eye with the exception of senile lens opacities were excluded [illegible] showed corneal oedema with epithelial bullae as indicated in the case [illegible] patients the actual corneal thickness had been measured on the first day of [illegible] by the doctor in charge or in some cases by the author Following the acute [illegible] were trabeculectomized or iridectomized on the affected side In the angle closure patients were a few months later iridectomized on the other side while the [illegible] patients were unoperated on the other eye at time of the present examination [illegible] were iridectomized on the other eye only three days prior to the exam[illegible] and pachometry readings were discarded in these patients while estimates [illegible] were not In the remainder the postoperative period for the control eye [illegible] more than two months

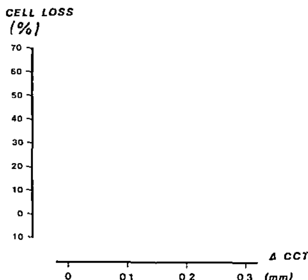


Fig 2

ıncrease ın central corneal thıckness (CCT) on the first day of admıssıon related to the ıated cell loss on the affected eye (Spearman s rank correlatıon coefficıent r_s − 0 68 *P* <0 05 n − 11)

day of admıssıon the ıncrease ın corneal thıckness on the affected sıde as pared to contralateral sıde was found to be sıgnıficantly correlated to the cell (Fıg 2) Attempts at correlatıng the cell loss to the vısual acuıty after the acute ck were unsuccessful

t the present follow up the corneal thıcknesses on the affected sıde were not erent from the unaffected sıde Mean central corneal thıckness (± SD) was 0 515 021 and 0 516 ± 0 026 mm respectıvely The corneal thıckness showed no ıd towards a gradual change versus tıme ın the post attack perıod studıed None wed epıthelıal oedema Mean ıntraocular pressure (± SD) was 18 2 ± 8 8 (range 2) and 16 5 ± 4 2 (range 12 26) mmHg on the affected an unaffected sıde pectıvely As can be seen the maın dıfference exısted ın the much larger varıatıon he ıntraocular presures found ın the eye wıth prevıous attack of acute glaucoma the ınter-eye dıfferences ın ıntraocular pressure were plotted agaınst the r-eye dıfferences ın central corneal thıckness a sıgnıficant negatıve correlatıon eared (Fıg 3) Thus ın thıs sıtuatıon where the patıents served as theır own ıtrols the ıntraocular pressure was found to decrease the corneal thıckness

Results

On the average the cell count on the side with previous attack of acute [illegible] 23.1% lower than the contralateral side with a large range in the [illegible] difference (Fig. 1). In the normal group the inter-eye difference was [illegible] a standard error of 5.7%. This means that 95% of the normal inter-eye [illegible] was less than 11.4% following the procedure of randomly choosing left [illegible] as reference. In this way 13 of the patients could be said to have sig[illegible] endothelial cell density on the affected side. The counts themselves [illegible] not show any definite grouping into normal and abnormal differences [illegible] taking the group as a whole the inter-eye differences were highly [illegible] different from zero. (A Wilcoxon test for paired differences showed P < [illegible]

The subgroup of acute haemorrhagic glaucomas showed a mean decrease [illegible] density of 16.4% (range 4 to 46%). In either group the cell loss was not [illegible] time after the attack.

Table 1 shows the cell counts obtained in 7 patients undergoing a [illegible] glaucoma operation. Mean change in cell counts were found to be −1.3[illegible] standard error of independent cell counts obtained with the present tech[illegible] previously been shown to be 3.7% (Olsen 1979). Using this figure and [illegible] normal distribution the 95% confidence limits for the observed mean [illegible] calculated to be −2.7 and +0.1% respectively. Thus no significant [illegible] occurred during the operation and if there was any it was very [illegible] indicates the cell loss depicted in Fig. 1 not to be iatrogenic but to be a [illegible] attack.

In those instances where corneal thickness measurements were availa[illegible]

Table I
Estimated endothelial cell density in 7 patients before and 3-5 mon[illegible] after [illegible] operation. Mean change in cell density is −1.3%

Patient No	Operation	Cell count before (cells/mm²)	After (cell/mm²)	[illegible]
1	iridectomy	1450	13[illegible]	
2	trabeculectomy	2378	[illegible]	
3	iridectomy	2825	[illegible]	
4	trabeculectomy	1697	16[illegible]	
5	trabeculectomy	3003	[illegible]	
6	trabeculectomy	2609	[illegible]	
7	trabeculectomy	3059	[illegible]	

fore strongly indicative of the irreversible cell loss having occurred during the attack of glaucoma The results of Svedberg (1975) suggest that the pressure may destroy the endothelial layer but it may be suggested that additional rs such as speed of onset ischemia and anaerobic metabolism due to impaired of aqueous may also contribute to the endothelial damage

e endothelial damage had important consequences on the corneal hydration as n in Fig 2 It was not tried to correlate the duration of the attack and the actual r tension to the cell loss due to difficulty in precise determinations of these bles It may be suggested however that the cellular destruction was the final non path of these variables to increase the corneal hydration

ine (1956) noted an association between a low number of endothelial cells and endency of the cornea to become oedematous at increased intraocular ure He concluded however the low cell density as such to be the cause of the rmal hydration The results of the present study indicate that it is the active c-down of cells that matters It is remarkable that even if more than 50% of the s had been destroyed it did not seem to have a permanent effect on corneal ation Mean corneal thickness of the previously attacked eye was found not to r from the unaffected eye The latter result is in accordance with other authors e 1969 De Cevallos et al 1976)

the present follow up examination the patients turned out to have a large tion in the intraocular pressure in the previously attacked eye Using the nts contralateral eye as control the intraocular pressure was shown to be rsely correlated to the corneal thickness (Fig 3) In interpreting these results it portant to remember that the patients at this time had an intact endothelium as imented by the intact endothelial reflex (Fig 4) During the acute attack with ased corneal thickness it has never in hands of the author been possible to n in a normal endothelial reflex (Fig 5)

he results of the present study therefore indicate that the intraocular pressure eases corneal thickness if the endothelial layer is damaged but decreases the neal thickness if the endothelial layer is preserved The hypothesis that the state the endothelium may switch the thickness response of the cornea in either ction has been suspected by some authors (Mishima 1968 Ehlers 1970) but not umented

animal experiments Ytteborg & Dohlman (1965) suggested that the increased aocular pressure might have damaged the endothelium for the increased kness to occur The clinical data reported by these authors (Ytteborg & hlman 1965a) are however inconclusive on that point since many of their ents must have had secondary glaucoma where damage to the endothelium via r routes (operation inflammation) cannot be ruled out (Olson & Kaufman 8)



Fig 4

The en[illegible]helial reflex in a patient with a previous attack of unilateral ang[illegible] closure [illegible]coma. Top: Endothelium of affected eye. Estimated cell density [illegible] cells/mm[illegible] Bottom: Endothelium of normal fellow eye. Estimated cell density [illegible] mm². Bar indicates 100 μm

ıe fact that the cornea with intact endothelium thins in response to elevated ıocular pressure raises some theoretical questions as to the function of the othelium in this situation If the endothelium was highly impermeable to water ould be understandable that an increased pressure gradient across the cornea ld make it thin The endothelium has however failed to demonstrate such an ermability to water in the rabbit (Mishima & Hedbys 1967) and in the human nley 1972) *The fact that the cornea does not swell in vivo has therefore called* he existence of an active endothelial pump which constantly pumps fluid out of stroma into the aqueous (Mishima 1968 Maurice 1969 1972 Hodson & Miller 5) On basis of this model a very leaky endothelium and a large pumping ity the hydration of the cornea would be expected to increase if the pressure lient across the endothelium was raised

ı view of the present findings and other reports showing an inverse relationship een IOP and corneal thickness at presumed intact endothelium (Ehlers & Riise 7 Ehlers 1970 Olson & Kaufman 1978) it seems that if the pump-leak concept the function of the endothelium is to be maintained it would require the pump e activated or the leakage to be lowered in response to an increased intraocular ssure as long as the pressure does not damage the endothelium

Acknowledgments

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References

rne W M & Kaufman H E (1976) Cataract extraction and the corneal endothelium *mer J Ophthal 82* 44–47

ndler P A & Grant W M (1965) Lectures on glaucoma Philadelphia p 166 Lea & ebiger

Cevallos E Dohlman C H & Reinhart W J (1976) Corneal thickness in glaucoma *Ann phthal 8* 177–189

ers N (1970) On corneal thickness and intraocular pressure II *Acta ophthal (Kbh) 48* 107–1112

ers N & Riise D (1967) On corneal thickness and intraocular pressure *Acta ophthal (Kbh)* 5 809–813

ers N & Sperling S (1977) A technical improvement of the Haag Streit pachometer *Acta phthal (Kbh) 55* 333–336

enne R (1969) Les glaucoma 1 von p 353

Forstot S L, Blackwell W L, Jaffe N S & Kaufman H E (1977) The effect of lens implantation on the corneal endothelium. Trans Amer Acad Ophthal Otol 19?–203

Harris J E, Gersitz L & Gruber L (19?) The hydration of the cornea II ... intraocular pressure. Amer J Ophthal 42 ?32–3?9

Hodson S & Miller F (1976) The bicarbonate ion pump which regulates the ... rabbit cornea. J Physiol 26? ?63–5?7

Irvine A R (19?6) The role of the endothelium in bullous keratopathy ... (Chicago) 56 338–3?1

Kaufman H E, Capella J A & Robbins J E (196?) The human corneal endo... J Ophthal 61 83?–841

Leber T (1873) Studien Über den Flussigkeitswechel im Auge ... Ophthal 19 87–1?5

Lowe R F (1969) Central corneal thickness ocular correlations in normal eyes ... primary angle closure glaucoma. Brit J Ophthal 53 824–826

Maurice D M (1969) The cornea and sclera. In: The Eye. Davson H (ed) ... 489–600. Academic Press, London & N Y

Maurice D M (1972) The location of the fluid pump in the cornea. J Physiol ...

Maurice D M & Hoefle F B cited in Kaye C I, Sibley R C & Hoefle F B ... studies on the nature and function of the corneal endothelial barrier. Exp ... ?8?–?1

Mayes K R & Hodson S (1978) Some effects of hydrostatic pressure on corneal ... during ... lar microscopy. Exp Eye Res 26 141–145

Mishima ... (19?8) Corneal thickness. Surv Ophthal 13 ?7–9?

Mishima ... & Hedbys B O (1967) The permeability of the corneal endo... ...thelium to water. Exp Eye Res 6 10–32

Olsen T (19?9) Non-contact specular microscopy of human corneal endothelium ... (Kbh) 57 9?6–998

Olsen R J & Kaufman H E (1978) Intraocular pressure and corneal ... penetrating keratoplasty. Amer J Ophthal 86 97–100

Rao N C, Shaw E L, Arthur F & Aquavella J V (197?) Morphological ... healing corneal endothelium. Arch Ophthal (Chicago) 96 2027–2030

Sbordone C (1953) Richerche sullo spessore della cornea in occhi glaucomatosi ... 2? 262–268

Stanley J A (1972) Water permeability of the human cornea. Arch Ophthal ... ?8–?73

Stoker F W (1971) The endothelium of the cornea and its clinical implications ... C Thomas, Springfield Ill

Svedberg B (1975) Effect of artificial intraocular pressure elevation on the corneal endothelium in the vervet monkey. Acta ophthal (Kbh) 53 83?–8?5

Ytteborg J & Dohlman C H (196?) Corneal oedema and intraocular pressure I ... experiments. Arch Ophthal (Chicago) 74 375–381

Ytteborg J & Dohlman C H (196?a) Corneal oedema and intraocular pressure ... results. Arch Ophthal (Chicago) 74 477–484

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ENDOTHELIAL CELL DENSITIES IN DONOR AND RECIPIENT TISSUE AFTER KERATOPLASTY

BY

PEKKA RUUSUVAARA

A specular microscope was used to photograph the cell densities of the central cornea of the graft and the peripheral recipient cornea in a total of 32 human eyes The follow up period varied from 8 months to 13 years with an average of 4 7 years

The mean endothelial cell count in the graft was 997 ± 356 cells/mm² and 1410 ± 584 cells mm² in the recipient s peripheral cornea. The mean difference in cell counts between donor and recipient tissues was 413 ± 718 cells/mm² (29%)

There were great disparities between graft and recipient cell densities One patient with keratoconus had a graft/recipient differential in cell density of 3 to 1 In four cases the cell density was higher in the graft than in the recipient. Of these grafts two had been stored in M K medium and two had been cryopreserved The great difference in cell density observed between the graft and recipient corneas strongly suggests that little if any cell migration occurs between graft and recipient. This suggests that the scar tissue forms a barrier to cell migration between graft and recipient.

Key words endothelium – cell density – cell migration – corneal graft – corneal preservation – contact specular microscopy

ntaneous division of corneal endothelial cells has not been demonstrated to ır in man In a study of eye bank eyes a rare mitosis was observed in othelium stained with para nitro-blue tetrazolium (Kaufman et al 1966) Da ed human endothelium is believed to heal by spreading and sliding of the aining live cells to cover the areas of dead cells and not by cell division This

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presumably explains the larger corneal endothelial cells and lower cell observed after certain operative procedures

In 1968 Maurice developed a specular microscope for studying the endothelium Laing et al (1975) and Bourne & Kaufman (1976a) [illegible] instrument for clinical use and since then much information has been [illegible] about the behaviour of the human corneal endothelium

In their specular microscope studies Blackwell et al (1977) and [illegible] (1978) showed that the human cornea has similar cell counts at the [illegible] periphery and that pairs of eyes have similar axial cell counts likewise [illegible] of normal eyes Laule et al (1978) found that in most cases counts of the [illegible] cell population of one eye are closely correlated with the corresponding [illegible] of the fellow eye

In view of the restricted capacity of the human endothelium to divide [illegible] the cell densities and cell morphology in corneas to be used for human [illegible] very valuable A question of the utmost importance is the origin of the [illegible] cells that are present in a human corneal graft after long term follow [illegible] speculation exists about the capacity of human endothelial cells to [illegible] from the graft to the recipient or conversely from the recipient to the graft [illegible] Brown 19[illegible] Bourne & Kaufman 1976c Polack 1977)

The purpose of this paper is to compare the endothelial cell densities of corneal grafts with those of the peripheral recipient cornea A conclusion [illegible] about the question of whether human endothelial cell migration occurs [illegible] donor and recipient tissue sites

Patients and Methods

I have previously presented a clinical series comprising 102 penetrating keratoplasties in 9[illegible] patients (Ruusuvaara 1979 a b) The patients of the present [illegible] subgroup of that series comprising 32 penetrating keratoplasties in [illegible] these grafts 6 were bilateral The follow up period varied from 8 months [illegible] years with an average of 4 7 years The ages of the patients ranged from [illegible] years and those of the donors from 13 to 78 years The ratio of males to females 3 to 1

There were altogether 31 eyes with keratoconus and one patient had [illegible] dystrophy A contact specular microscope (Seyber Inc) was used to photograph the central cornea of the graft and the recipient cells at the periphery [illegible] peripheral endothelium of the unoperated fellow eye was also photographed [illegible] obtain photographs of the cornea at the centre and periphery a fixation [illegible]

…d to the wall This enabled the patients to maintain the appropriate gaze Eye …n was also checked by intermittent direct observation of the eye The …teral recipient cornea was photographed in the nasal and temporal areas …ssible For each eye 10 to 20 photographs were taken at the periphery and …centre of the cornea and 5 of the clearest from each area were selected for …g and counting The prints had a final magnification of x 500

…ive methods

…perations were mostly performed by the same two surgeons The size of the … was 7 mm in 20 cases and 8 mm in the rest Operative methods and …ments used are described in an earlier paper (Ruusuvaara 1979a)

…ds of corneal preservation

…atients were grouped according to the method of preservation of the donor …as One group comprised 11 patients with grafts which had been stored in a … chamber as whole globes at 4 C for less than 48 h

… donor corneas were transplanted after an intermediate term of preservation …lays) in the M K medium (McCarey & Kaufman 1974) Cryopreservation …man & Capella 1968) had been used for 16 donor corneas with a preservation …rom 8 days to 4 years

Results

…ll 39 patients the mean endothelial cell count in the graft was 997 ± 356 …mm² (Table I) The mean endothelial cell density in the recipient periphery …410 ± 584 cells/mm² The mean difference in endothelial cell counts between …r and recipient tissues was 413 ± 718 cells mm² (29%) In the 8 patients in …n the periphery of the fellow eye was also photographed the endothelial cell …ty in the periphery of the operated recipient eye was 1742 ± 688 cells/mm² …en that of the fellow eye 2918 ± 310 cells/mm² the unoperated eye having 68% … cells at the periphery than the operated eye

…rther analysis of cell densities in graft endothelia showed that grafts had …ficantly more cells after storage in M K medium than after cryopreservation or …ge in a moist chamber Moreover of the two latter groups the cryopreserved …ts had significantly more endothelial cells ($P < 0.001$) The follow up period …longest (8½ years) for the corneas grafted after moist chamber storage and …at the same (2¼ years) for cryopreserved corneas and corneas stored in M K …ium

Patient	Preservation method	Donor age (years)	Cadaver time	Preservation time	Follow up period	Mean cell density of grafts (cells/mm²)	Mean cell density of recipient peripheral endothelia (cells/mm²)	% of difference	Fellow eye cell count (cells/mm²)
1	cryo	47	6 h	1 mo	3 yrs 7 mo	963	1217	21	3067
2	–	47	0	1 mo 29 d	1 yrs 5 mo	858	1275	33	–
3	–	[illegible]	2 h	4 mo 23 d	4 yrs 2 mo	842	1133	11	–
4	–	72	0	8 mo 1 d	2 yrs 2 mo	[illegible]	2508	62	3292
5	–	66	0	2 yrs 11 mo	9 mo	1133	1400	19	–
6	–	[illegible]	9 h	[illegible] mo 21 d	3 yrs 11 mo	1325	925	−13	–
7		70	[illegible] h	11 mo 29 d	1 yrs 9 mo	[illegible]	1138	7	–
8	–	73	[illegible] h	2 yrs 3 mo	11 mo	[illegible]	[illegible]	6	–
9	–	[illegible]	2 h	11 d	3 yrs 6 mo	[illegible]	1135	18	–
10	–	72	0	3 yrs 11 mo	10 mo	1333	1708	[illegible]	–
11	–	55	0	[illegible]	[illegible]	1138	[illegible]	2	–
[illegible]	–	[illegible]	0	[illegible]	[illegible]	1000	[illegible]	[illegible]	–
[illegible]	–	[illegible]	[illegible]	[illegible]	[illegible]	1070	[illegible]	[illegible]	–
[illegible]	–	–	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	–
[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

	moist chamber								
17	–	50	13 h	3 h	8 yrs 4 mo	650	121	18	[illegible]
18	–	4	22 h	1 h	8 yrs 9 mo	808	1033	22	–
19	–	25	11 h	1 h	6 yrs 5 mo	675	908	26	–
20	–	18	3 h	21 h	6 yrs 6 mo	[illegible]0	2702	80	2912
21	–	36	15 h	1 h	8 yrs 5 mo	975	1258	30	–
22	–	–	0	1 h	1 yrs 11 mo	958	1267	24	–
23	–	54	1 h	9 h	6 yrs 11 mo	863	883	2	–
24	–	38	5 h	24 h	5 yrs 11 mo	712	1233	10	2858
25	–	62	3 h	–	10 yrs 9 mo	612	917	21	–
26	–	69	2 h	48 h	8 yrs	917	992	8	–
27	–	10	12 h	2 h	12 yrs	737	1113	34	–
Total (moist chamber)	11	34	8 h	11 h	8 ½ yrs	765±129*	1231±543*	38%	–
	M K media								
28	–	35	3 h	4 d	3 yrs 6 mo	1012	1283	19	–
29	–	29	5 h	4 d	2 yrs 5 mo	77[illegible]	1292	40	2933
30	–	31	0	3 d	3 yrs 6 mo	2103	7[illegible]0	–131	–
31	–	29	[illegible] h	3 d	2 yrs 5 mo	912	2333	60	3153
32	–	39	1 h	[illegible]	1 yrs 7 mo	217[illegible]	1266	– 72	[illegible]
Total (M K)	[illegible]	33	3 h	3 d	2 ¾ yrs	1403±6 6*	139 ± 08*	±0	–
All cases	3[illegible]	13	1 ½ h	–	4 7	997±356*	1410±581*	29%	2918±310*

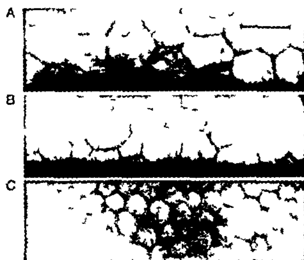


Fig 1A B C (patient no 17)

Specular micrographs of corneal endothelium A Graft (preserved by moist chamber for 3 h) B peripheral endothelium of recipient C peripheral endothel[illegible] of [illegible] Cell densities of graft recipient and fellow eye are 650 mm² 1?1? mm² and [illegible] 2?0 bar 50 μ)

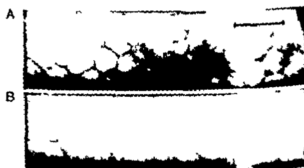


Fig 2A B (patient no 30)

A Central corneal endothelium of a graft stored in M K medium for 3 days B [illegible] endothelium of recipient Cell den ities of graft and recipient are ?10? mm² and [illegible] ?50 bar 50 μ)



Fig 3A B (patient no 12)
l corneal endothelium of a graft cryopreserved for 1 year and 2 months
ral endothelium of recipient with clearly dystrophic endothelial cells (Fuchs) Cell
nsities of graft and recipient are 1000/mm² and 69ɔ/mm² (x 2ɔ0 bar 50 µ)

dothelial cell densities at the periphery of the recipient corneas did not
ıficantly from each other in the different preservation groups although
ents of grafts stored in a moist chamber had 300 fewer cells/mm² than the
of cryopreserved grafts ($P > 0$ 0ɔ) Thus it seems that the differences in
lation density between the graft and the peripheral recipient cornea are
ıt mainly on the cell density of the corneal graft itself the difference
graft and recipient being greatest in the group that had received grafts
a moist chamber In this group the difference in cell density between graft
ient was 466 ± 613 cells/mm² which means that the peripheral recipient
ad 72% more endothelial cells than the graft In 5 grafts stored in M K
there was no difference in average cell densities between graft and
In the 16 cryopreserved corneal grafts the cell density in the recipient
al cornea was 55' higher than in the graft
ınd recipient cell densities showed great disparities (Fig 1A B C) One
ıth keratoconus (pa ient No 30) had a graft/recipient differential of 3 to 1
B)
ıgh in most cases the cell density was higher in the recipient tissue in four
as higher in the graft Two of these grafts had been stored in M K medium
l 3 days (Fig 2A B) two had been cryopreserved One of the latter was in
nt with Fuchs dystrophy (patient No 12) (Fig 3A B) No dystrophic cells
ınd in the graft whereas nearly all the peripheral endothelial cells were
dystrophic with non reflecting areas

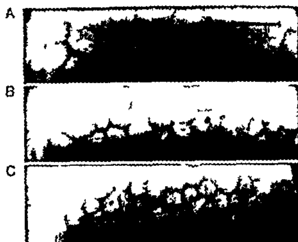


Fig 4A B C (patient n 20)

A Central corneal endothelium of a graft preserved by moist chamber 4 h B the recipient endothelium and C peripheral endothelium of fellow eye Cell density of recipient and fellow eye are 550 mm² 2799/mm² and 2913 mm²

The maximal difference in cell density between graft and recipient was for patient with keratoconus (patient No 20) This donor graft had been in moist chamber and there had been an episode of graft rejection 3 years after operation The graft cell density was 550 cells/mm² and the recipient 2792 cells/mm² a difference of 1 to 5 (Fig 4A B C)

Table I shows the mean donor age cadaver time preservation time period mean cell densities of grafts and recipients in each individual of different preservation groups

Discussion

In human studies there has been speculation but few actual data are available on the migration or spread of endothelial cells from the recipient to the graft or in the opposite direction (Bourne & Kaufman 1976c) Bron & Brown (1974) suggested that a given percentage of non viable cells in the donor cornea must be replaced by sliding of cells from the recipient They also believed that in Fuchs dystrophy for example where the viability of the recipient cells is already questionable cells might migrate from graft to recipient especially with larger grafts In a patient with an 11 month-old clear penetrating corneal transplant Bourne & Kaufman (1976b) observed a significant increase in endothelial cell density above

...ase They believed that the increased number of central endothelial cells must ...arisen either by cell division or by sliding of cells from the periphery of the ...or from the recipient tissue

...cular microscopy after keratoplasty shows a uniform cell density within the ...l clear graft portion of the endothelium (Laing et al. 1976) The cell density ...n the recipient portion is likewise uniform. Yet it is reasonable to assume that ...time of surgery cell loss will vary from one area to another It will probably be ...est at the centre of the graft, which may be pressed against the iris and lens ...ally when the anterior chamber is shallow and along the peripheries of both ...and recipient tissues where suturing would be accompanied by localized ...ia.

...imal studies have shown that rabbit donor endothelium can repopulate the ...ient cornea when there is a deficiency of recipient endothelial cells. This was ...d by Olson & Levenson (1977) using sex chromatin as cell marker Bourne ...) in his study with monkeys concluded that more cells of the recipient type are ...ally found in the periphery than in the central part of the graft. He took this ...dence of cellular migration from host to graft. In other studies (Gospodarowicz ... 1979) no invasion of the corneal button by the recipient endothelial cells and ...ersely no invasion of the recipient endothelium by the donor cells could be ...d in bovine or rabbit transplants.

...my study comparison of the cell densities in the corneal graft and the ...pheral recipient cornea showed very great disparities. In most cases the cell ...ity was found to be much lower in the graft than in the recipient. The ...rence was highest (550 2792 cells mm²) in a patient with keratoconus who had ...a rejection episode in the transplant 2 years before photography It seems ...onable to assume that if in his case any cells had migrated from the peripheral ...e of the recipient to the graft the differences in cell densities would not have ...so great (a differential of 1 5) Also in the patient with Fuchs dystrophy all the ...t cells were hexagonal and normal-looking and all the peripheral recipient cells ...typically dystrophic. So no normal cells seemed to have migrated from the ...splant to the dystrophic recipient area.

...eight cases it was possible to compare the peripheral endothelia of the ...rated eye and its fellow The mean difference in cell density between the ...rated and *unoperated eye was more than 1000 cells mm². Thus it seems that in* ...atoplasty we lose an average of 41% of cells from the recipient peripheral ...othelium. Thus in performing keratoplasty one must remember that the ...pient corneal endothelium is also vulnerable and may suffer later complications ...n operative damage

...ccording to this study it seems that little if any cell migration occurs between ...or and recipient tissues. Supporting this view is the observation of great disparity

between population densities in both directions across the donor re... in some cases it was the graft and not the recipient cornea tha had ... density In those cases in wh ch the endothelial cell densities of gra... were virtually the same we can speculate that cells were also lo... peripheral cornea during the surgical manipulation especially the ... suturing Although it seems that endothelial cells can slide w... the graft and within that of the peripheral recip ent cornea to cover the ... this study strongly suggests that no cell migration occurs across the ... between graft and recipient

References

Blackwell W L Cra enstein N & Kaufman H E (197) Comparison of ... endoth elial cell numbers with peripheral areas *Amer J Ophthal 84* ...

Bourne W M (197) In vi o survival of cryopreserved endothelial ... *O ... Chicago 97* 146 148

Bourne W M & Kaufman H E (1976a) Specular micr scopy of human ... *Amer J Ophthal 81* 319–32

B urne W M & Kaufman H E (1976b) Cataract extraction and the ... *Amer J O hthal 82* 44–47

... ne W M & Kaufman H E (1976c) The end thel um of clea ... *(Chicago)94* 1730 1732

B n A J & Brown N A P (1974) Endothel um of the corneal graft ... *94* 863 873

Gospodarowicz D Greenburg G & Alvarado J (197) Tran plantation of ... corneal endothelial cells to rabbit c rnea Cl nical implications ... *Acad Sci Wash* 6 481 489

Kaufman H E & Capella J A (1968) Preserved c rneal tissue ... *Ginn u g I* 125 130

Kaufman H E & Capella J A & Robbins J E (1966 The human corneal ... *Amer J Oph hal 61* 835 841

Laing R A Sandstr m M Berrospi A R & Leibow tz H M (197 ... *corneal endothelial cells after penetrating keratoplasty* ... *Amer J Ophthal* ...

La ng R A Sandstr m M & Leibowitz H M (1975 In vivo pho ... corneal endothel um *A h O hthal (Chicago) 93* 143 14...

Laule A Cable M K Hoffman C E & Hanna C (1978) End thelial ... of human cornea during l fe *A h O hthal (Chicago)* 96 2031 2035

McCarey B E & Kaufman H E (1974) Improved c neal ... 1...

Maurice D M 1968 Cellular membrane act its in th corneal endothe ... *eye Experientia Basel* 24 1094 109...

O son R J & Levenson J E (197) M gration of donor e dothel ... *O h hal 94* ... 11 ... 14

F M (1977) *Corneal Transplantation* pp 45–69 Grune & Stratton New York.
vaara P (1979a) Effects of corneal preservation donor age cadaver time and
-operative period on the graft endothelium *Acta ophthal. (Kbh.)* 57 868–881
vaara P (1979b) Histocompatibility and corneal graft endothelium *Acta ophthal. (Kbh.)*
968–981
ck G D Sherrard E S & Rice N S C. (1978) Specular microscopy of the corneal
othelium *Brit. J Ophthal.* 62 809–814

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ENDOTHELIAL CELL DENSITY IN DONOR CORNEA

BY

STEFFEN SPERLING

In 58 pairs of donor corneas the endothelial cells were visualized by provoked swelling of the cell borders in isotonic saline. In corneas from donors ... years of age numerical cell density was correlated to age. This was not the case in corneas from older donors. The cell densities in paired corneas were correlated. The cell density in the second cornea of a pair was found ... within x̄ ± 10.97% (±1.99 SD) of the first cornea. The precision of this estimate could only be improved insignificantly by correction for age, sex, ... density or variation of the mean.

Key words: human cornea – endothelial density – contralateral cornea – unbiased counting

If the demand for donor corneas with high endothelial cell density cannot be met by the supply from young donors, available tissue from older donors can be ... individual evaluation. If a direct view of the endothelium has been obscured by corneal oedema, or if a specular microscope is not available, the endothelial cell density can be determined in an excised cornea by an ordinary light microscope after provoked swelling of the endothelial cell borders in ... (Sperling & Larsen 1979).

This study was undertaken in order to evaluate the precision of an estimate of endothelial cell density in a donor cornea, based on observations in the contralateral cornea, and in order to evaluate whether knowledge of donor age or sex ... to the precision of the estimate.

Received October 10, 1979

Material and Methods

hundred and thirty six cadaver corneas from 34 patients of each sex aged from 15 to 92 were included in the present study Whole eyes were enucleated when no history of eye se appeared from the case record and when the conjunctiva the cornea and the anterior ent appeared normal by simple inspection Enucleated eyes were discarded when signs lammation trauma or surgery were found by slit lamp examination

rneas were prepared with a scleral rim and the endothelial cell borders were visualized rovoked swelling in isotonic saline (Sperling & Larsen 1979) Microphotographs were ned at a total linear magnification of 162 x on Polaroid type 667 8 3 × 10 8 cm The oscope was set at random within the central 6 mm of cornea and three photographs were ned when two thirds or more of a full field could be brought in focus Two photographs selected on basis of the largest photographic clarity On each photograph cells were ted in two test frames of 16 5 × 32 5 mm The procedure of unbiased counting ibed by Sperling & Gundersen (1978) was applied

Results

each cornea the sex the mean endothelial cell density ($\bar{x}$) the standard deviation ne mean (SD($\bar{x}$)) and the coefficient of variation (CV ($\bar{x}$)) = $\frac{SD(\bar{x})\ 100}{\bar{x}}$) was regi

d For each pair of corneas the relative difference between contralateral mean cell sities ($D_r = \frac{|\bar{x}_1 - \bar{x}_2|\ 100}{\bar{x}_1}$) was determined One cornea of each pair was chosen at dom as cornea 1 without regard to original right left situation The mean ies and some correlations between the registered parameters are indicated in le I As no difference was found between male and female corneas the fficients of correlation are also indicated for the total material comprising 68 s In 68 paired values correlation is significant ($2P < 0\ 05$) when $r > |0\ 245|$ cumenta Geigy 1970)

highly significant correlation was found between cell densities in paired neas ($r = +0\ 94$ $n = 68$ $2P < 0\ 001$) In the total material the coefficient of relation between age and cell density ($\bar{x}_1$) was $-0\ 27$ ($0\ 025 < 2P < 0\ 05$ $n = 68$) l density was correlated negatively to age in 18 corneas from 9 donors of less n 50 years of age ($r = -0\ 62$ $n = 18$ $0\ 005 < 2P < 0\ 01$) while this was not the in 118 corneas from 59 older donors ($r = +0\ 06$ $n = 118$) A negative relation was also found between the cell densities and the relative differences) between mean densities of paired corneas ($r = -0\ 30$ $n = 68$ $0\ 025 < 2P <$ 5) The correlations between the relative difference and age and between the ative difference and coefficient of variation (CV (x)) were just below significant ues ($r = 0\ 23$ and $r = 0\ 22$ respectively $2P > 0\ 05$)

Table I

Correlations between mean cell density ($\bar{x}$), coefficient of variation on the mean (CV ($\bar{x}$)), relative difference between mean cell densities in contralateral corneas (D) and donor age

x, y	Sex	$\bar{x}$/$\bar{y}$	r_{xy} (n = 31)	r_{xy} (n = [illegible])
x_1, x	M	2912 21 2937 38	0 93	0 94
	F	2726 00 2728 97	0 95	
D, x_1	M	3 09 2932 21	−0 18	−0 30
	F	4 53 2659 00	−0 28	
D, age	M	4 00 65 75	0 ·	0 23
	F	4 53 61 00	0 23	
D, CV ($\bar{x}$)	M	4 00 4,59	0 30	0 2
	F	4 50 3 88	0 15	
x_1, age	M	2932 21 65 76	−0	−0 [illegible]
	F	2726 00 61 00	−0 30	

The distribution of relative differences between contralateral mean cell [illegible] is shown in Fig 2 On probability paper the differences showed a close [illegible] to a normal distribution When the differences were arbitrarily [illegible] positive and negative values a mean value of −0 35 and a standard dev[illegible] was found This indicates that the cell density in the second cornea of a pa[illegible] within the interval x ± 10 97 (± 1 98SD) with a probability of [illegible] Yates 1957)

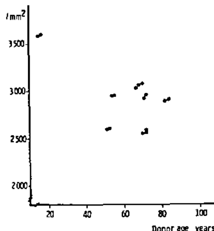


Fig 1

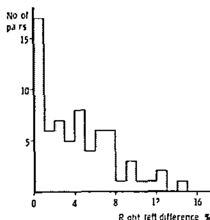


Fig 2

1 Central endothelial cell density related to age for one cornea from each of 68 pairs

2 Distribution of relative differences between contralateral endothelial mean cell ısities $\left(\frac{|\bar{x}_1-\bar{x}_2|\ 100\%}{x_1}\right)$

Comments

e corneas in the present study were selected by criteria applied for donor terial Corneas were obtained from the hospital morgue without regard to ient age The overrepresentation of corneas from patients over 50 years of age %) reflects the high incidence of older patients dying in the hospital

n the present material a strong positive correlation was found between endothelial l densities in paired corneas This indicates that the second cornea of a pair can accepted or excluded for individual evaluation when the endothelial cell density known in the first cornea The tendencies towards decreasing correlation with with low numerical cell density and with variation of the mean were weak This licates that the precision of an estimate of the endothelial density in the second rnea of a pair can only be improved slightly by correction for donor age mean l density or variation of the mean

In the present material endothelial cell density was negatively correlated to donor e when the total material was considered A strong correlation appeared in 18 rneas from young donors while no correlation ($r = +0\,06$) was found in 118 rneas from donors of more than 50 years of age This indicates that whenever

donor tissue with high endothelial density is wanted there is no reason [illegible]
younger of two donors over 50 years of age

Endothelial cell density have earlier been related to age by Irvine & Irv[illegible] Bourne & Kaufman (1976) Laing et al (1976) Laule et al (1978) Sperl[illegible] Sturrock et al (1978) Olsen (1979) In the data published by most of the[illegible] negative correlations between age and endothelial cell density were f[illegible] group 0 50 years In corneas from older individuals age and cell dens[illegible] *correlated in either material*

Acknowledgments

This study was supported by grants mediated by the Danish Committee f[illegible] Blindness The Danish Medical Research Council and Institute of Experim[illegible] Research University of Aarhus Laboratory technician Mrs B Olesen Dep[illegible] Ophthalmology Århus Kommunehospital

References

Bourne W M & Kaufman H F (1976) Specular microscopy of human corneal [illegible] in vivo *Amer J Ophthal 81* 319–323

Documenta Geigy (1970) *Scientific tables* 7 ed Diem K & Lentner C (Eds) J R [illegible] Basle

Fisher R A & Yates F (1957) *Statistical tables for biological agricultural and med[illegible]* Oliver & Boyd London

Irvine R & Irvine R jr (1953) Variations in normal human corneal endothel[illegible] *Oph hal 36* 1279–1285

Laing R A Sandstrom M M Berrospi A R & Leibowitz H M (1976) [illegible] corneal endothelium as a function of age *Exp Eye Res* 22 587–594

Laule A Cable M K Hoffman C F & Hanna C (1978) *Arch [illegible]* [illegible] 2031–2035

Olsen T (1979) Non-contact specular microscopy of human corneal end[illegible] *[illegible]thal (Kbh)* 57 996–998

Sperling S (1978) Indirect evaluation of corneal endothelial cell density [illegible] 56 [illegible]

Sperling S & Gundersen H J G (1978) The precision of unbiased estimates of densities of endothelial cells in donor corneas *Acta ophthal (Kbh)* 56 [illegible]

Sperling S & Larsen I (1979) Toxicity of dimethyl sulfoxide (DMSO) to [illegible] endothelium in vitro *Acta ophthal (Kbh)* 57 891–898

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DIABETIC RETINOPATHY IN VISUAL DEPRIVATION

A case report

BY

LUTZA YANKO

A case of asymmetric retinal involvement in a diabetic patient who has long been exposed to visual deprivation on one eye is described The question implied by this condition is if a relationship could exist between the distinct exposure of each eye to different visual excitations and the outcome of the different retinal diabetic involvement The possibility that the retina in a resting state might be less prone to develop diabetic retinopathy than usual and a possible functional hypothesis on the pathogenesis of this diabetic complication are questioned

Key words diabetic retinopathy – asymmetry – visual depri ation

lower than expected prevalence of diabetic retinopathy has often been reported i patients in whom other ocular conditions were present In some circumstances a egative association has been observed between increased intraocular pressure and ie development of diabetic retinopathy particularly proliferative retinopathy ome of the work relating to this association between ocular tension and retin pathy has been reviewed by Keen (1972) and by Shin et al (1977) Other different cular conditions accompanying retinal sparing have also been described occasio ally in diabetics

Clinical observations of asymmetric retinal involvement particularly when associ ted with other significant intraocular differences might be of some value in nvestigating possible causal associations and the pathogenesis of diabetic retin pathy

Received May 29 1979

Department of Ophthalmology (Head O Odd) Fylkessjukehuset i Aust Agder A endal, Nr

ACUTE OCULAR HYPOTONY AS A MANIFESTATION OF MUMPS

A Case Report

BY

JON ERIK SLAGSVOLD

A 27 year-old woman with epidemic parotitis developed acute hypotony in her right eye This complication is not mentioned in earlier reports concerning this disease She also suffered from keratitis and iritis The inflammatory reaction of the anterior eye subsided on topical medication but the hypotony persisted for two weeks Factors possibly influencing the low intraocular tension are discussed

Key words epidemic parotitis – keratitis iritis – ocular hypotony

Case Report

A 27 year-old housewife was admitted to the Eye Clinic with two days history of pain, red and increasing hazy vision in her right eye There was no history of previous eye disease. She had been exposed to mumps through affected family members i e two daughters and father none of whom had eye problems Five days before admission she had developed characteristic swelling of both parotid glands

Eye examination disclosed normal physical findings of her left eye The right eye showed moderate ciliary injection oedematous corneal epithelium opaque stroma and folds in Descemet s membrane (Fig 1) Cornea was about twice as thick as in the fellow eye (pachometry) Slit lamp examination of the anterior chamber revealed a trace of flare and cells some fine corneal precipitates The pupil had a normal size and reacted briskly. Visual acuity was 6/24 corrected The intraocular tension measured with Goldmann applanation tonometry was 10 mmHg (left eye 14 mmHg) The eye was treated with atropine and prednisolone acetate 0 5% five times daily

Received October 1 1979

F g 1
eye showing central opaque parenchyma and folds in Descemet s membrane



F g 2
nt look ng downwards to show the impress on of enophthalmos (ptisis) caused by the hypotony

Five days later the corneal oedema persisted but the vision had improved 6/12 The eye however was so soft that it gave the impression of enophthalmos (Fig 2) i e ... tonometry 4 mmHg (Schiøtz 14/5 5) Glycerol eye drops temporarily removed ... oedema whereafter gonioscopic and funduscopic investigations with the three-mirror (Goldmann) were performed No pathological changes were observed in retina or iridocorneal angle

During the following three weeks all symptoms subsided The enophthalmos ... the visual acuity and the intraocular pressure gradually normalized (6/6 11 mmHg) Descemet s folds remained for three and a half months Further follow up for ... showed normal intraocular tension

Mumps serology not analyzed in family members confirmed the clinical diagnosis increase from 80 to 160 in seven weeks (complement fixation test)

Discussion

The diagnosis of mumps was based upon medical history (family members) ... examination (parotid swellings) virus serology and leaves no doubt in this case

Several ocular manifestations in mumps are known i e dacryoadenitis, ... tivitis keratitis uveitis scleritis optic neuritis (Stenstrøm 1943 Blix 19... 1953 Katavisto 1956 Riffenburgh 1961) Five cases of glaucoma have described (Stenstrøm 1943 Roussel 1946 Riffenburgh 1954 Polland & Th... 1976) Hypotony as a complication to mumps has to my knowledge never reported previously

The patient suffered from corneal oedema, iritis and hypotony Corneal ... ment in parotitis is exceedingly rare (Fields 1947) but represents a ... characteristic clinical picture (Riffenburgh 1961) i e usually unilateral ... developing keratitis profunda with complete clearing The iritis is usually a serous inflammation probably self limited leaving no synechiae visual loss or sequelae The findings in our case fits well with these descriptions The ... corneal oedema could neither be explained by the mild iritis nor the hyp... which persisted for many days after the cornea had cleared up

As to the cause of the hypotony different pathogenetic factors may be ... Intraocular pressure is influenced by the central nervous system ... glaucoma has been observed in cases of meningitis of other origin ... induction caused by mump virus in this case leading to low pressure ... unlikely i e the patient had no signs of meningeal inflammation

Detachment of the retina or choroid may be associated with hypotony ... 1954) With maximal dilatation of the pupil paying special attention to the ... periphery these conditions were ruled out

Iridocyclitis is often accompanied by low intraocular pressure The inflam...

n of the anterior chamber was mild and subsided rapidly However the ony may be explained by a more specific affection of the secretory function of iary body On the other hand Chandler & Maumenee (1961) found fluid n the sclera and the ciliary body in eyes with mushy soft tension following clitis These eyes however suffered from a heavy inflammation which was e case in our patient

otony without any obvious explanation following another viral eye disease rpes zoster was reported by Juler (1928) He suggested that atrophy of the body might be responsible

References

(1952) Fall av øgonkomplikasjoner vid parotit Nord Med 48 1593–1594

ler P & Maumenee A E (1961) A major cause of hypotony *Amer J Ophthal 52* –618

J (1947) Ocular manifestation of mumps A case of mumps keratitis *Amer J Ophthal* 91–595

\ (1954) Acute hypotonia *Brit J Ophthal 38* 364–368

F (1928) Hypotony following herpes zoster ophthalmicus with lid suture *Trans hal Soc U.K 48* 179–180

sto M (1956) Eye complications of epidemic parotitis *Acta Ophthal (Kbh) 34* 208–213

D P (1953) Ocular complications of mumps *Brit J Ophthal 37* 99–101

d W & Thorburn W (1976) Transient glaucoma as a manifestation of mumps A case rt *Acta Ophthal (Kbh.) 54* 779–782

burg R S (1954) Iritis and glaucoma associated with mumps *Arch. Ophthal (Chicago)* 102

burg R. S (1961) Ocular manifestations of mumps *Arch Ophthal (Chicago) 66* –743

l F (1946) Une complication rare des oreillons (uveits) *Rev Med. Liege 1* 305

röm S (1943) En sallsynt øgonkomplikasjon vid parotitis epidemica *Nord Med. 20* 1–2459

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Short Communication

IMPROVEMENT OF CONTRAST SENSITIVITY FROM TREATMENT FOR AMBLYOPIA

BY

GUNNAR LENNERSTRAND and BJÖRN L. LUNDH

Twenty four amblyopic children were treated with grating visual stimulation In eight of them visual acuity did not change However four of these eight children showed improved contrast sensitivity

Key words contrast sensitivity – visuogram – amblyopia – CAM treatment

We have studied contrast sensitivity changes during treatment for amb[illegible] children and correlated them to changes in visual acuity Monocular [illegible] sensitivity of both the good and the amblyopic eye was established before and [illegible] amblyopia treatment in children aged 5½ to 13 years The method was [illegible] that used by Derefeldt et al (1979) except that only one determination of [illegible] threshold was made at each spatial frequency Amblyopia was treated [illegible] method of grating visual stimulation described by Campbell et al (19[illegible] deprived eye was exposed to high contrast grating patterns of different [illegible] frequencies while the good eye was occluded Treatment periods of ten [illegible] were repeated twice a week Between sessions the children continued to wear best spectacle correction If no improvement of visual acuity was found after [illegible] sessions the good eye was part time occluded e g all the time the child [illegible] from school Most children showed some increase of visual acuity for far and [illegible]

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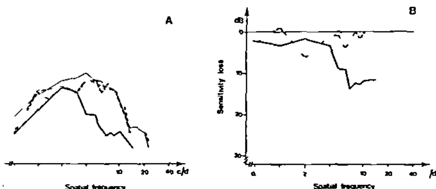


Fig 1

ges in contrast sensitivity from amblyopia treatment of the right eye of a ten year-old ith anisohypermetropia and right microtropia. Snellen visual acuity was 0 2 of the right nd 0 8 of the left eye before and after fifteen sessions of grating pattern stimulation

ontrast sensitivity curves of both eyes before (full line) and after treatment (dashed line) hicker lines notify the amblyopic right eye The maximal contrast available was 43%

isuogram showing the left eye before (full line) and after treatment (dashed line) The ast sensitivity at each spatial frequency has been related to values obtained in normal of children aged 6 to 10 years (see Derefeldt et al 1979) This sensitivity loss is expressed 3 After amblyopia treatment the sensitivity loss is less marked in the 4 to 10 cycles per ee range

in quite a few cases visual acuity remained at the same level even after fifteen ons and parttime occlusion In the group with improved visual acuity parallel iges were seen in the contrast sensitivity More remarkable was the finding that eases of contrast sensitivity also occurred in children regarded as failures from standpoint of visual acuity only An example is given in Fig 1 This ten year old with anisometropia and microtropia had a Snellen acuity of 0 2 before and r treatment of his right amblyopic eye However after ten training sessions the trast sensitivity of this eye showed a marked increase in the range of middle and 1 spatial frequencies (Fig 1A) This is also illustrated with the visuogram of his blyopic eye (Fig 1B) Similar results have been obtained in four out of eight dren who showed no change in visual acuity

hus improvement of contrast sensitivity from amblyopia treatment, without ct on visual acuity has been clearly demonstrated in children These results phasize the importance of contrast sensitivity determination in the evaluation of blyopia (Hess 1979) and in amblyopia treatment Undoubtedly a normalisation ontrast sensitivity even for a restricted range of spatial frequencies represents a table gain in the visual ability of an amblyopic eye

References

Campbell F W Hess R F Watson P G & Banks R (1978) Prel m nary re physiologically based treatment of amblyopia *Brit J Ophthal 62* 748 55

Derefeldt G Lennerstrand G & Lundh B (1979) Age variat ons in normal human sensitivity *Acta ophthal (Kbh) 57* 679–690

Hess R (1979) Strabismus and anisometrop c amblyop a *Au tr J Optom 62* 4 19

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TRANSACTIONS OF THE DANISH OPHTHALMOLOGICAL SOCIETY 1977–1978

BY

ERIK SCHERFIG Secretary

471st Meeting October 1 1977 in Copenhagen (Rigshospitalet)

te Warburg *Blindness among 7742 mentally retarded children in Denmark. o-medical aspects)*

e have performed a screening among 7742 mentally retarded children below 21 years of and have examined 385 individuals suspected of being blind. Blindness was found in 82% hem. After the completion of the examinations reports on blind children were still ncoming. The blind M. R. children observed represent 50% of all blind Danish children mildly retarded children make up at least 8% of the total group of normal educationally normal and mildly retarded blind children in Denmark. The majority are severely or oundly retarded (60%). Epilepsy was found in 70% spastic palsy in 61% and hearing rders in 14%. Of the children 37% could walk, 40% could sit in chairs while 19% could lie down. Optic atrophy cortical blindness tapeto-retinal degeneration and cataract e the most common diagnoses retrolental fibroplasia was less frequent than among other d children.

he principal causes of blindness were brain disorders a genetic aetiology was disclosed in infections in 13% and prematurity without oxygen treatment in 6%.

lindness had not been recognized in one third of the group prior to this study. We suspect this has led to considerable under stimulation.

cussion *H. Skydsgaard E. Goldschmidt S. Ry Andersen*

S. Norn *Chamber depth before and after cataract extraction*

n a total of 80 patients with senile cataract the anterior eye chamber dept was measured ically by means of Haag Streit s attachment II. The distance to the lower pupillary border preoperatively 2.59 ± 0.05 mm (mean ± SEM). After cataract extraction it gradually reased to 3.33 ± 0.04 mm measured four months after the operation. The increase of oth was greatest in patients with a flat chamber and in elderly patients.

The central chamber depth gradually *decreased* after the operation (from 2 81 ± preoperatively to 1 95 ± 0 13 mm four months postoperatively)

The number of vitreous prolapse cases rose from 68 to 88 per cent in four ... possible causes were discussed

(Published 1978 in Brit J Ophthal *62* 474–477)

Discussion *S V Kessing K K Dresler S Ry Andersen and Jens Edmund*

Niels Vesti Nielsen and Per Nellemann Sørensen *Fluorescein angiography for borderline diabetes mellitus*

Fluorescein angiography of the retina was performed in 54 persons with an abnormal 2 hour glucose tolerance test and in 23 controls with a normal glucose tolerance. Microaneurysms were found in 48% of the series with a reduced glucose tolerance and leakage from microaneurysms in 43% of those having microaneurysms. Of the normal group 13% had microaneurysms but no leakage. Within both series ophthalmoscopy showed no microaneurysms and no signs of diabetic retinopathy. There was no relationship between ... and the number of microaneurysms in the group with abnormal glucose tolerance. On the other hand there was a correlation between inherited predisposition to diabetes and the occurrence of microaneurysms whereas smoking was of no importance. The results support the assumption that diabetic microangiopathy may already develop before diabetes mellitus becomes manifest

Discussion *H W Larsen M Warburg S Ry Andersen T Deckert (guest) E Goers Rosenberg E Godtfredsen*

Jens Edmund *Vitrectomy method – results – indications*

Discussion *N Ehlers H Skydsgaard T Deckert (guest) E Dresler E Gregersen P N ... H W Larsen S Ry Andersen P Brændstrup E Goldschmidt*

Eilif Gregersen J Pontoppidan and E Rindziunski *Intra and ... variations in atropine resistant residual accommodation*

Accommodation is an extremely persistent reflex which has a marked resting ... Therefore it is difficult if not impossible to abolish accommodation completely. This is reflected in the concept residual accommodation i e the accommodation remaining after application of a cycloplegic. The problems relating to residual accommodation ... phenomena such as depth of field and tolerance of blur which have been reported ... a varying order of magnitude from one-quarter to one dioptre

Among 25 amblyopic patients with esotropia who were treated in the course of ...zation therapy with atropine 1% once daily into the dominant eye for about one year ... showed residual accommodation of ≧ 2 dioptres in the dominant eye. Thereafter the ... atropine was increaed to 1% twice daily up to 2% twice or thrice daily in an attempt to ... the residual accommodation

Summing up it must be emphasized that in some patients long term instillation of ... can induce only partial not total cycloplegia. In such patients the atropine resistant ...

ımodation shows pronounced ınter and ıntra ındıvıdual varıatıons wıth amplıtudes from dioptres as well as a sporad c and constant occurrence The most marked atropıne-ınt res dual accommodation was observed in two children who were "bookworms" ugh at retinoscopy the patient is usually bl nded by the light from the retinoscope and fore does not use his residual accommodation during the retinoscopy procedure it is ways poss ble to rule out a few or many dioptres of accommodation during retinoscopy r cycloplegia.

ol shed *in extenso* in Transactions of the Th rd Meeting of the International Strabismolo-Association Kyoto Japan, 1978

ıss on *P B ændstrup O Hartkopp N Ehlers E Goldschmidt V D ever*

General Meeting October 1 1977 in Copenhagen (Rigshospitalet) with M S Norn in the Chair

rts were subm tted from the Board comm ttees and commissioners

e General Meeting requested the com ng to work out a report on visual and ocular care nmark.

e following were elected for the new Board Eil f Gregersen (President) Erik Krogh *I Mortensen Erik Presler and Erik Scherf g (Secretary)*

472nd Meeting December 3 1977 in Copenhagen (Rigshospitalet)

nical pathological conference arranged by the Univers ty Institute of Ophthalmic *ology*

Andersen O A. Jensen Jan Ulrik Prause

Feen cases were elucidated f rst by a brief clinical survey and thereafter by a pathological onstration

473rd Meeting February 24 1978 at Scanticon Århus

um Memorial Lecture

essor G Mackensen Freiburg *Microsu gical techniques and pathogenetic knowledge*

fessor Mackensen ga e an inspiring memorial lecture on the development of microsur technique in ophthalmology He stressed that after a trauma the surgery should be ed out as soon as possible and that complete reconstruction of the injured eye must be ormed at the primary operation

Postgraduate Course February 25 and 26 1978 at Scanticon Århus

Teachers Professor Benjamin Milder St. Louis Missouri Professor Robert D L..
Albany New York
In charge of the course Thomas Rosenberg
Subject Refraction
Basic book *R Reinecke & R Herm* Refraction a Programmed Text Appleton-Cr..
Crofts New York 1976
In 10 sessions followed by discussions selected parts of the refraction proble..
elucidated in theory and in practice

Guest Lecture, February 25 1978 at Scanticon Århus

Professor Lalit P Agarwal New Delhi India *Prevention of blindness in India*

In an extremely thought provoking paper Professor Agarwal reviewed the ca..
blindness in India and described the organization of the efforts to prevent bl..
including those of DANIDA

474th Meeting April 15 1978 in Copenhagen (Rigshospitalet)

Mette Warburg *Congenital retinal malformations simulating retrolental fibroplasia*

Congenital retinal non attachment (C N S) and falciform folds (C F F) may be the ..
of environmental influences in foetal life such as viral infections or X-radiation ..
malformations may also occur in various chromosomal aberrations localized ..
non attachment may be found at the margin of colobomata of the choroid and ..
genetic mutations may give rise to C F F of C N A

Autosomal dominant mutations are rarely responsible for C F F or C N A, ..
reports of both types have been published Autosomal recessive inheritance of ..
malformations may be either confined to the eye or be part of complex syndromes ..
events C F F and C N A may alternate in the two eyes of each affected individual and ..
eyes of affected members of a sibship Several complex syndromes have been descri..
Saraux s syndrome with C N A osteoporosis and hypotonia (2) microcephaly micro..
mos and congenital C F F (3) the Meckel syndrome and (4) hydrocephalus micro..
mos and C N A

There are also X linked complex syndromes with C N A or C F F i e Norrie's dise..
the Bloch Sulzberger type of incontinentia pigmenti

In all genetic disorders and particularly in autosomal recessive disorders pati..
appear as solitary cases and the C F F and C N A in such patients will show malfor..
indistinguishable from retrolental fibroplasia In patients with these malforma..
sporadic appearance of one of the syndromes listed above should be considered b..

-osis of retinopathy of prematurity is made in full term infants who have been treated oxygen

ussion *J Edmund S Ry Andersen H Skydsgaard P Brændstrup N Willumsen E rsen*

Madsen *Experience of the transportable photocoagulator Log 2*

o years ago the Eye Department Roskilde acquired a transportable Xenon photocoagu Log-2 from the firm Clinitex The price was 55 355 Danish kroner +value added tax

is photocoagulator has been used for a number of different purposes and has proved ient in practically all cases even in very fair patients with faint pigmentation of the us and of the iris

e only patients who could not be treated with the Xenon photocoagulator were those a very small pupil less than 5-6 mm and patients with quite peripheral changes

e treatment factors were Power 5-6 for 0 5-1 sec. Diaphragm 4-4 5 for macular lesions 5 for the retinal periphery

ere have been no complications of the treatments in particular no bleeding from the al vessels

a rule the patients were under retrobulbar anaesthesia but in a few the treatment could erformed without anaesthesia.

mong the last 50 patients treated with photocoagulation there were 15 diabetics some simple and some with proliferative retinopathy

hese patients were treated partly with peripheral coagulation partly directly onto the ns This applied in particular to the proliferative changes

ourteen patients with an exudative maculopathy the majority senile changes a few ral serous retinitis Our treatment was partly horseshoe-shaped coagulation at the edge of oedematous area but later treatment was given centrally directly onto the oozing points

ven had venous thrombi central vein occlusion or branch vein occlusion with macular nges In such cases the coagulation was directed along the vessels in the involved areas

en patients had retinal detachment retinal tears or retinoschisis In these cases the tment was partly at the edge of the retinoschisis and retinal detachment and partly tment of the retinal tears

n addition four cases of small or displaced pupils in aphakic eyes were treated with tocoagulation

onclusion The Log 2 photocoagulator is easy to operate and very handy It is easily nsported from one room to the other It has sufficient power to afford reaction in light di and in oedematous and somewhat detached retinal areas in senile maculopathy and t completely attached retinal detachments It was also effective in the treatment of placed irides

scussion *E Gregersen O Nissen*

Nellemann Sørensen Niels Vesti Nielsen and Knud Nørskov *Ocular rtension A 15-year follow up*

ublished 1978 in *Acta Ophthal. (Kbh) 56* 363–372

ussion *E Gregersen, O Nissen*

S Rv Andersen M Warburg P Geertinger H W Larsen M Miller-Parving and S Vestermark *The deletion p 11 syndrome anirudia urogenital ... and mental deficiency*

The case of a 21 month-old girl the second child in a family without known ... or malformation was reported

The child had bilateral aniridia cataract and mental deficiency Chromosomal ... revealed a small interstitial deletion with band p12 and p13 on the short arm of ... 11 missing Karyotype 46 XX del (11) (pter→p13 p11→qter)

Both parents and a half brother had normal karyotypes Thus the child ... anomaly is considered to be a new mutation X-chromatin was present, but no ... was found and the child had female external genitalia The face was ... micrognathia low-set ears and mild coloboma of the nares The fundus of the ... of normal appearance (the left one could not be visualized because of dense cata... girl died of pneumonia following measles

Microscopy disclosed bilateral benign gonadoblastomas in small gonadal streaks ... sign of Wilms tumour or of abnormal embryonal renal structures ... of both eyes revealed typical aniridia no iris muscles and no anterior cleavage ... Both lenses were small and cataractous The pigment epithelium of the retina was ... disintegrated in places and in the right eye some of the peripheal retinal vessels ... occluded Small retinal strands proliferated into the vitreous in this area No ... papillo-macular bundle could be identified

In the literature three patients with deletion of the short arm of chromosome 11 ... mental deficiency and genital malformation have been described by Francke et al ... *them harboured a Wilms tumour* Ladda et al have described a patient with aniridia ... tumour and interstitial deletion of the short arm of chromosome 8 In our opinion ... most likely from chromosome 11

One patient with aniridia gonadoblastoma and genital malformation but without ... somal studies has been reported by Gracia et al and DiGeorge et al described a ... gonadoblastoma aniridia and Wilms tumour

We feel that the cases reported so far including our own ... of a syndrome with partial deletion of the short arm of chromosome 11 aniridia and ... or genital dysmorphogenesis

References

DiGeorge A M & Harley R D Arch Ophthal. 1966 75 796–798
Francke U George D L Brown M G & Riccardi V M Cytogenet. Cell Genet ... 197–207
Gracia R Nieto J A Nistal M Iturriaga R Lledo G Barrio R & Lama R ... Pediat. 1976 9 suppl 8 19–24
Ladd R Atkins L Littlefield J Neurath P & Marimuthu K M Science 197... 784–787

Discussion *P Brøndstrup E Krogh.*

I

Thygesen Per Reersted Hans Fledelıus and Leıf Corydon *Astıgmatısm ataract extraction Late results after corneal ıncısıon and corneo scleral ıncısıon respectıv ely blıshed 1979 ın Acta ophthal. (Kbh) 57 243–2ɔ1*

ussıon *K K Dresler N Bulou M Hesse E Gregersen S Barner*

⁽ⁱ N orn *Spheroı l degeneratıon of the cornea and conjunctıv a*
ıshed 1978 and 19ı9 ın Acta ophthal (Kbh) *56* 5ɔ1–562 and *57* 96–10ɔ

‹ussıon *I Dreyer S Rı Andersen K K Dreısler O A. Jensen P Alsbırk E Skeller A Jørgensen N Wıllumsen P Brændstrup*

ᵞ Prause *Antıproteases and collagenase ın human lacrımal fluıd Methodol ıcal problems and a ‹ntatıon of a neu mıcro-ımmunoelectrophoretıc method*

ᶠfter a brıef presentatıon of the accepted mode of *ın vıvo* destructıon of corneal stroma ˙ lvıng tıssue collagenases the more specıfıc balance between the serum antıproteases ᶠıa 1 antıtrypsın alpha 1 antıchvmotrypsın and alpha ² macroglobulın on the one hand polymorphonuclear leukocyte collagenase (PML-collagenase) on the other was descrıbed ˜v thıs method the author avoıded the many errors due to organ culture by measurıng ›protease and the PLM-collegenase ın lacrımal fluıd from patıents wıth corneal ulcers
s PLM-collegenase ıs found only ın mınute amounts ın lacrımal fluıd a mıcromodıfıcatıon he electroımmunoassav of Laurell has been elaborated (1) Usıng thıs assav and a rabbıt ˀhuman leukocyte collagenase (2) ıt has been possıble to detect the named balance ın ɛrımal fluıd from patıents wıth corneal ulcers
˜he materıal ıs beıng prepared for publıcatıon ın an extended form ın Acta Ophthalmologıca

erences

ıuse J L Sjostrom H Noren O & Josefsson L (19 8) A mıcromodıfıcatıon of the lectroımmunoassav Anal Bıochem *85* 564–ɔ71
ılsson K & Olsson (1973) The neutral proteases of human granulocytes Eur J Bıochem *36* 473–481

ɔ dıscussıon

Gregersen and J U Prause *Corneal perforatıon after the El more pıll blıshed ın Acta ophthal (Kbh.)*

ıscussıon *I Dreyer M Wa bu g S Rı An lersen N W llumsen S Asboe J Thygesen K K eısler J Boberg An*

Brændstrup *Open angle glaucoma burden of patıent and doctor*

hom J Zımmermann Louısıana State Unıversıty (ın ıted as a guest through the harmaceutıcal company Merck Sharpe & Dohme)
ım l l mal ate A neu gla oma medıcatıon

Herbert E Kaufman Louisiana State University (invited as a guest the pharmaceutical company Merck Sharpe & Dohme)
Timolol maleate A new glaucoma medication.

Niels Vesti Nielsen *Timolol for the treatment of intraocular hypertension (beta-blocking)*

Published 1978 in Acta ophthal (Kbh) *56* 504–509

E Gregersen and S Kessing *Short term effect of timol l as a supplement medication of glaucoma*

Discussion of the last five papers with contributions concerning the long indication for timolol therapy was recorded on a tape by Merck, Sharpe & Dohme

TRANSACTIONS OF THE SWEDISH OPHTHALMOLOGICAL SOCIETY 1978

EDITED BY

GUNNAR LENNERSTRAND

Meeting in Huddinge June 2–3 1978
General Session

oller & P Enoksson *Congenital ocular moto apraxia*

Iolm *A new high power microscope for studies of the anterior segment of the l nn human eye*

andard corneal microscopes do not permit a higher magnification than 25–40× They herefore of limited use in studies of cellular structures Such studies however have me increasingly interesting also in routine clinical work it is e g important to know the ition of the endothelial cell layer of the cornea before performing certain intraocular ical interventions

struments for studies of the corneal endothelium have been available for some time but require physical contact with the cornea and do not enable studies of deeper structures new high power microscope attachement has been developed It can be used with any g Streit type corneal microscope It utilizes regular slit illumination and does not require act with the eye The focus can be varied from the surface of the cornea to the anterior ace of the lens The magnification can be varied between 100 and 250 x

odifications for use on Zeiss slit lamps and for photography are being developed

ith this instrument called EMS 1 studies can be made of e g corneal epithelial and othelial cells lens capsular cells capsular exfoliations etc

Germanis *Some ophthalmological observations on children with reading difficulties*

omplete ophthalmologic examination including orthoptic investigation was done on 110 ool children who were referred to an ophthalmologist because of delayed reading ability of them were given remedial teaching No attempts were made to differentiate the group primary and secondary reading retardation

binocular disorders causing subjective complaints at the reading distance were looked for paired binocularity was revealed in 35% of the children and half of them complained of henopia blurring of vision or diplopia The binocularity disorders present and their

relative incidences were exophoria 9% esophoria 4% tropia 4% fusional de[illegible] accommodative insufficiency 8% From 6 prism dioptres exophoria to 4 prism [illegible] esophoria was considered as orthophoria. Most of the heterophorias present were [illegible] phorias

Most prone to subjective complaints were exophorias accompanied by [illegible] deficiency and the cases with accommodative insufficiency The latter was [illegible] changing and for the age remote near point of accommodation In half of the [illegible] poor accommodation was associated with hyperopia and low grade esophoria [illegible] helped with glass correction In the other half the accommodative insuffi[illegible] accompanied by convergence deficiency and most case histories revealed emotional [illegible] ces or subclinical systemic disease

The importance of measuring the near point of accommodation as well as the near p[illegible] convergence is stressed when dealing with problems at the reading distance

M Gjotterberg *Photocoagulation of Macular Diseases*

Macular lesions complicated by fluid leakage or neovascularisation are sometimes [illegible] to treatment by photocoagulation The indications for treatment of the [illegible] diseases are discussed and slides of typical cases presented

1 Central serous retinopathy The main factors when considering treatment [illegible] complaints of the patient and the location of the leak Coagulation of a point [illegible] periphery of the macula is a very safe procedure which significantly shortens the [illegible]

2 Exudative senile macular degeneration Detachment of the pigment epi[illegible] sometimes the initial event and may be treated The rationale of the treatment [illegible] prevent the development of cicatricial stages

3 Branch vein occlusion Some patients develop macular oedema which may lead [illegible] degenerations The hypoxia may cause neovascularisation These cases with [illegible] unfavourable prognosis are candidates for treatment

4 *Diabetic maculopathy Treatment of patients with oedema and or neovascularisa[illegible]* often beneficial

The main problem when considering photocoagulation treatment of macular lesions [illegible] how to treat but when to treat The unpredictable course of the involutional d[illegible] lack of controlled studies as well as the palliative nature of the treatment are all fact[illegible] render the assessment of the therapeutical results difficult

I Aringer *Chlamydia trachomatis in iritis and acute eye infections.*

This study was initiated from the connection between iritis and ankylosing spondyl[illegible] was started in 1975 with a study of the presence of chlamydia trachomatis in iritis [illegible] were taken from the conjunctiva of 12 patients with acute iritis Chlamydia was demonst[illegible] *in two of the patients Both were healthy except for their iritis*

Serum samples from 38 patients with acute iritis were sent for analysis to the [illegible] Virol lab Gothenburg Group specific chlamydia antibodies were demonstrated [illegible] patients (24%) Analysis of serum from controls that has been made at the same [illegible] has shown group specific chlamydia antibodies in 13% of the samples Of the 38 pa[illegible] had ankylosing spondylitis and two prostatitis but none of them were positive [illegible] previous history of urinary or genital tract infection four of them were positive [illegible] antibodies Five of the 9 patients that were positive were healthy except for their [illegible] Samples from the conjunctiva were also taken but they did not survive the transport

oles were also taken from the conjunctiva of 102 patients with a wide variety of acute tions They were analysed by doc C-O Kindmark and dr Rolf Zimmerman Virol Natl bact lab Stockholm In five of these patients chlamydia trachomatis could be ted from sample from conjunctiva One of them had recurrent dacryocystis two had rons one had acute and one chronic conjunctivitis One of the chalazion patients ed spontaneously whereas the other four patients had not improved during 2–3 s observation time They recovered quickly when treated with tetracycline

sions Chlamydia trachomatis has been shown to be present in various types of acute eye ons In this material patients from which chlamydia had been cultivated had shown a e tendency toward a prolonged illness The serum samples from the patients with iritis d a higher incidence of chlamydia antibodies compared to controls This higher nce cannot be explained by a history of ankylosing spondylitis or prostatitis

Symposium The Eye in Diabetes

rator *B Zetterstrom–Ka pe*

l members *S Stenkula M Gjotterberg P Algvere S Blomdahl J Cristiansson N Ma en s B Phil psson M Pandolfi*

jotterberg *Altered blood flow properties in the diabetic et na*

eview over the current hypotheses behind retinal hypoxia was presented Among the ple contributory factors suggested alterations in blood flow properties are stressed

gvere & B Kornacki *Fluorescein angiography of the iris in diabetic eyes* *phthal (Kbh) 56* 803–816 1978

omdahl & M Gjotterberg *The human el ctroreti ogram followi g photocoagulation*

istiansson *Diabetic retinopathy and pregnancy*

a total of 94 763 obstetric patients at the Central Hospital in Kristianstad 78 diabetics detected All except five of them were checked as to the influence of pregnancy upon eventual diabetic retinopathy Thirty five patients (48%) with an average diabetic tion of 15–16 years showed ophthalmoscopic signs of diabetic retinopathy In se en of the retinopathy progressed during pregnancy Ten patients (14%) had severe prolifera etinopathy of whom five actually developed this condition during pregnancy these 10 cases induced abortion was performed in two cases The remaining eight ers gave birth to six surviving children After delivery some reversion of proliferative opathy was observed in all cases often with a remarkable reduction of intra-retinal ilar tufts

ophylactic treatment by Scatter Xenon photocoagulation seemed of value in one case of eral elevated vascular neoformation The left eye was treated before pregnancy and d four years later The Snellen visual acu ty was 0 7 The non treated eye showed nized vitreous haemorrhage and a Snellen visual acuity of 0 1

In conclusion the incidence of diabetes in pregnant women is steadily increa- 0 3% in the present population The frequency of severe retinopathy is also ar- putting a strong demand on ophthalmic services

Preventive photocoagulation should seriously be considered whenever progre- towards a proliferative stage that will endanger vision

N Maren & Gjotterberg *Diabetic retinopathy and cigarette smokin*

S Boos *Sensitivity to dazzling light of diabetics during driving in darkness*

In order to ascertain whether persons with diabetes mellitus have impaired rea in the dark the readaptation time (RAT) after dazzling light has been measured T were compared with those of non–diabetics

Method The persons taking part in the experiment were made dark adapted in tru testfield with the luminance of 0 1 cd/m² A round object with the diameter of 1º was moving forward and backward horizonetally A dazzling light of 0,5 lux was p for 1 4 and 16 seconds It subtended an angle pursuit eye movements

Results All diabetics fullfilled the requirements for a Swedish driving licence and had a visual acuity of 1 0 Visual acuity in the dark (luminance 0 1 cd m²) was 0 diabetics and 0 6 for the non–diabetics The diabetics with retinopathy showed a longer RAT After a dazzling light of 1 second RAT was 2 7 second for t second for the normal group

After a dazzling light of 4 and 16 second respectively the values were second for the diabetics and 1 0 second for the non–diabetics

Conclusion This preliminary study shows that the diabetics with retinopathy impaired visual functions in darkness when driving a car by night, even if they h good visual acuity

P Algvere *Vitrectomy and excision of preretinal proliferations in diabetic sequel e*

To be Published 1979 in *Acta ophthal (Kbh) 57* 530 549

M Pandolfi & S Stenkula *Induction of fibrin dissolution in the vitreous body*

Injection of urokinase (a fibrinolytic activator derived from human urine) has been proposed as a treatment of intraocular haemorrhages On the basis of a rev literature and of own experiments both on animals and in vitro the authors dre following conclusions

1) The urokinase used hitherto can be purified further and has often been give doses

2) The optimal dose to cause a maximum fibrinolysis in the eye is probably m that used until now

3) The therapeutic effect it any of such a treatment is due to the fibrin proteolytic activity of the plasmin formed

Meeting in Sundsvall September 29–30 1978

osium *Visual field testing in glaucoma*

rator *L. Frisen.*

members *M Lundstrom P Enoksson H Brynke C Holmin*

sen *The pathophysiology of visual field defects in glaucoma*

sen *The tangent screen examination*

General Session

nderson & J Sjostrand *The function of the macula following retinal detachment involving macula*

aim of the present investigation was to evaluate different macular functions during ery following operation for retinal detachment involving the macula

hods Among all retinal detachment patients during a two and a half year period its (7) were selected meeting the following criteria visual acuity > 0 3 clear ocular absence of diabetes or previous macular disease The following parameters were d postoperatively (6 months to 3 years following operation) Visual acuity contrast ivity grating acuity micropsia and metamorphopsia.

ast sensitivity was measured using a TV monitor displaying a vertical sine wave grating m of variable spatial frequency and contrast (Sjostrand & Frisen *Acta ophthal. (Kbh) 55* 514 1977) Test distance was 5 m

ng acuity is a measure of the capacity to resolve a grating pattern A vertical sine wave ng pattern was displayed with the same equipment as used for the contrast sensitivity minations Test distance was 7 9 m and maximal contrst was used

c opsia Six out of the seven patients studied had micropsia The digree of micropsia was tified with an instrument constructed by L. Frisen

tamorphopsia Five of the patients had metamorphopsia It was tested by using the ler s grid

ts Contrast sensitivity In a group of patients examined more than a year following achment an abnormal contrast sensitivity function could be observed in two age groups high and intermediate frequency ranges were affected predominantly Currently we are ying the spatial precessing preoperatively and during the recovery phase Preoperati ely in the early phase following operation the contrast sensitivity is impaired over the whole uency range with a successive improvement during recovery

ating acuity In the patients examined the grating acuity showed a tendency to be higher atients with a recovery period of more than two years No correlation between time of operative macular detachment and postoperative grating acuity was found in the patients died However in this retrospective group of patients it was difficult to define the time of operative detachment

Micropsia. The micropsia ratio (ratio between size of the image in the eye with retinal tachment and fellow eye respectively) was 0 71 0 91 Some of the patients had a marked ropsia even a long time after operation The micropsia was not correlated to the visual ity The cause of the micropsia is presumably a changed distribution of photoreceptors to persistent macular oedema or proliferation of glial tissue

Metamorphopsia A varying degree of metamorphopsia was observed In some cas correlation between the results of the Amsler s test and the funduscopic changes wa

Conclusion The postoperative macular function after reattachment of the mac abnormal for a long period of time and various functions can be differently affected

P Algvere *Pars plana vitrectomy in amyloidosis Report of a case*

Primary systemic amyloidosis with peripheral neuropathy and ischaemic [illegible] disease was found in a male aged 66 and verified by a rectal biopsy He became b[illegible] on both eyes (only light projection) due to dense vitreous opacifications

An intracapsular cataract extraction was performed and 4 weeks later a pa vitrectomy (using Klott s vitreous stripper) enabled removal of the amyloid mate that the optical transparency of the eye was restored There was a rapid post recovery and in 2 weeks the visual acuity was 0 5 (aphakic correction) and in 8 [illegible] 1 0

At a follow up examination 10 months later the visual acuity was 1 0 the eye [illegible] inflammation and the vitreous space was clear there being no new formation of [illegible] material in the vitreous space The fellow eye was still blind

Pars plana vitrectomy yields good results in amyloid vitreous opacification and [illegible] several aspect superior to the open sky technique used earlier

L Frisen *Micropsia and macular oedema*

R A Ronnerstam *Occurrence of Chlamydia Trachomatis associated with external [illegible] eye A preliminary report*

The occurrence of Chlamydia Trachomatis has been investiga ed during a period [illegible] months in 101 patients treated at the department of Ophthalmology in Malmo [illegible] acute conjunctivitis and keratoconjunctivitis Six of these patients were newborn chil[illegible] found Chlamydia in four adults in fertile age with serious keratoconjunctivitis and [illegible] newborn children with conjunctivitis

These findings prompted a five months investigation of further [illegible] patien[illegible] symptoms of external ocular inflammation irrespective of age and serious ess of [illegible] In this clinical material Chlamydia was isolated only in one adult and two children [illegible] same period search for Chlamydia was made in all newborn children of this town [illegible] mothers Out of 600 infants one was found to have Chlamydia in the conjunctiva [illegible] mothers were found to have Chlamydia in the cervix uteri

During these seven months 28 newborn infants with conjunctivitis were examined [illegible] ophthalmic department In five of these the isolation of Chlamydia was positive [illegible] significantly higher frequnecy compared with 1/600

Chlamydia isolation might be of clinical importance since Chlamydia is known [illegible] pneumonitis and other infections in newborn children furthermore it may cause [illegible] in the mother

In Malmo we treat newborns with Chlamydia conjunctivitis with oral erythr[illegible] together with chloramphenicol or sulphonamides locally Also the mothers of [illegible] receive erythromycin while all other adults are given doxycyclin All patients have responded well to the treatment

dbergh A Bıll P Kaufman & E Lutjen Drecoll *Effects of Cytochalasın B and ı the anterıor segment of the eye*

cameral ınfusıon of Cytochalasın Bor EDTA (ethylenedıamınetetracetate) ın the lı ıng / eye elımınates about 3/4 of the total resıstance to aqueous humor outflow
›hologıcally Cytochalasın B causes a relaxatıon of the cells ın the crıbrıform meshwork ıs of the extracellular materıal and ruptures of the ınner wall of Schlemm s canal The endothelıum and cılıary body are also affected *(Invest Ophthal Vı Scı 17* 718 734

A breaks up the cell junctıons of the trabecular meshwork wıth loss of the extracellular ıl ın the crıbrıform area The ınner wall of Schlemm s canal balloons ınto the lumen or ›s In the corneal endothelıum the apıcal cell junctıons separate
physıologıcal effects are reversıble wıthın 1 ? h The morphologıcal effects of alasın B are reversıble wıthın 7 days Studıes of the healıng process after EDTA are ray

ttrell & M Pandolfı *Propranolol ı e sus aceta_olamıde A doublemasked study concernıng n ıntraocular presure a d system c blood pressure*

Walınder E B Hakansson & M Lındberg *Bl cadren (Tımolol) ophthalmıc ın the treatm nt of sımple and exfolıatıı e glaucoma a short term study*

adren (tımolol maleate) ıs a beta blockıng agent whıch as an ophthalmıc solutıon has ıtensıve effect on open angle glaucoma equal to 4% pılocarpıne It has nc serıous fects (Symposıum on Glaucoma XXIII Int Congress of Ophthal Kyoto 1978)

ıl Prevıously untreated chronıc open angle glaucoma

s An applanatıon pressure curve was performed 1–2 days before treatment was wıth 0 25% Blocadren eye drops x 2 If ıntraocular pressure (IOP) was not controlled mmHg) therapy was changed to 0 5% Bolcadren x ? and then addıtıon of 2–4% pıne acetazolamıde or the eye was operated upon

The study ıncluded 21 eyes ın 19 patıents mean age 67 years There were 5 sımple 5 exfolıatıve galucoma wıth an average IOP before treatment of 30 and 32 mmHg tıvely Fıfteen eyes had obvıous vısual fıeld defects and glaucomatous changes ın the the rest had suspected changes of the same kınd
adren caused a mean reductıon of IOP of about 40% ın the sımple glaucoma durıng a up of 3 months
exfolıatıve glaucoma (16) had a reductıon of IOP of about 40% durıng the fırst days en the hypotensıve effect of Blocadren decreased and only 3 eyes were controlled 5 months Nıne eyes requıred addıtıonal 2–4% pılocarpıne and one eye also requıred olamıde to be satısfactorıly controlled durıng a perıod of 3 months Operatıons were med ın three eyes
adren had a doubtful hypotensı e effect ın a patıent on propranolol 10 mg x 3 orally there was a slıght reductıon of IOP ın a patıent on alprenolol 0 1 g x?
adren caused no sıde-effects

usıons In thıs short term study Blocadren alone controlled IOP ın sımple glaucoma exfolıatı e glaucoma often requıred addıtıonal therapy

Meeting in Stockholm November 30 – December 1 197

General Session

G Lennerstrand *Structure of extraocular muscle in Siamese cats and domestic ca... unilateral lid closure*

We have previously reported differences in eye muscle functions between normal ... cats and cats with binocular defects (Siamese cats and domestic cats with monocular ... from age 2–3 weeks) Speed of muscle contraction and fatigue resistance was ... latter group The differences were most marked between normal and Siamese cats ... correlates to the functional changes were explored in histochemical experiments ... muscles that were examined physiologically Transversal muscle sections were ... myosine ATPase and succinic dehydrogenase Type I and II fibers were identif... proportions and distributions of the two fiber types were the same in all muscles ... succinic dehydrogenase content of the fiber populations was not significantly differ... of the groups of cats

However the total cross sectional area of the muscle was smaller in Siamese and ... cats than in normal cats due to a general decrease in size of both type I and II fibers ... the number of capillaries per muscle fiber was reduced in the Siamese and lid ... animals in comparison with normal cats

It is suggested that the decreased speed of contraction is correlated with the red... fiber size and the lowered fatigue resistance with the decreased capillary densit... Siamese and lid sutured animals These changes might represent muscular adaptation ... lack of binocular vision and to reduced demands for fusional vergence movements

M Pandolfi & E Lantz *Keratokinase the urokinase like plasminogen activator of the ...*

P Algvere & A Bill *Effects of lens removal and vitrectomy on drainage of particles fr... space*

The movements of plastic microspheres (7–10 µm in diameter) and radioactive ... red cells from the vitreous to the aqueous compartment were studied in vitrecto... non vitrectomized phakic and aphakic eyes of 18 rabbits The particles and red cells ... suspension) were injected into the centre of the vitreous space observed by ... and studied with histology and autoradiography

In phakic eyes the particles and red cells were unable to gain access to the ... chamber irrespective of whether a vitrectomy was performed or not Following lens ... and breaking of the anterior vitreous border microspheres and red cells reached the ... chamber and chamber angle within 2–10 days A combined lentectomy and ... resulted in rapid clearance of the vitreous space and large amounts of particles ... in the inferior chamber angle within a few days

The experiments indicate that the most effective clearing of blood from the ... occurs after a combined lentectomy and vitrectomy Following a vitrectomy alone ... anterior vitreous border still prevent particles from enterning the aqueous compar...

L Öhman L Berggren R Hahnenberger & E D B Johansson *The ... steroids (17β – oestradiol and progesterone) from the eye and nose to plasma and cerebro ...*

The free steroids norethindrone progesterone and 17β – oestradiol have been ... eye – drops or been given as drops or spray in the nose of rhesus monkeys ...

? mine the resorption to blood and cerebrospinal fluid The administered dose has been ? 1/2 mg steroid (1 drop in each eye or nostril of 1/2% or 5% suspension or solution ively) Blood and cerebrospinal fluid samples have been taken before the administra the drops and frequently during one h The steroids have been analysed by nmunoassay

— The free steroids are rapidly resorbed into the plasma e g in a couple of min the -ting levels of hormones increase several times The resorption is much better for ne in solution than in suspension Maximum levels of hormones in plasma are seen 5–30 min The levels of hormones in the cerebrospinal fluid are generally low

sion The three steroids are rapidly resorbed to plasma after ocular or nasal administra he levels of hormone in the cerebrospinal fluid are generally low

achtmeister & J Dowling *Microelectrode study of the oscillatory potentials of the et gram (ERG) of the mudpuppy*
Ophthal Vis Sci 1978 17 1176–1188

ostrand & I Burstyn *Contrast sensitivity in amblyopia*

ilateral amblyopia due to strabismus or anisometropia is in most cases treatable if ted at an early age With correction of refraction errors in combination with patching sual acuity is improved

e aim with our study was to analyze the contrast sensitivity function in patients (age years) with amblyopia due to strabismus or anisometropia with the following questions there any differences in contrast sensitivity functions between the two types of yopia can changes in the contrast sensitivity function be documented in children during ment

od The contrast sensitivity for sinusoidal gratings of varying contrast and frequency was rmined monocularly by raising contrast from a subthreshold setting until a grating rn was faintly seen With playing technique measurements could be done down to an of 5 years with good reproducibility

lts Children (age 5–9 years) were tested before and following treatment. The contrast sitivity curves of the non amblyopic eyes were within or slightly lower than those sured in adult normal subjects in an earlier study (J Sjostrand & L. Frisen Contrast itivity in macular disease A preliminary report *Acta Ophtal (Kbh.) 55 507–514 1977*)

A strabismic amblyopia (visual acuity 0 1–0 5) before treatment the contrast sensitivity for rmediary and low spatial frequencies was similar to that measured in the contralateral amblyopic eye and no effect of patching could be demonstrated in these spatial ranges in of improvement of visual acuity

n amblyopia due to anisometropia (visual acuity 0 1–0 2) the contrast sensitivity curves e drastically depressed before treatment and during patching treatment an improvement found in both contrast sensitivity and visual acuity

n young adults (age 15–31 years) with amblyopia (visual acuity 0 05–0 2) abnormal trast sensitivity was demonstrated in both strabismus and anisometropia However the nges were more marked in anisometropic amblyopia

Conclusion Contrast sensitivity studies can be carried out down to an age of a years determination of contrast sensitivity gives a more general information concerning the sensitivity gives a more general information concerning the spatial visual function than tests With sinusiodal gratings displayed on a TV screen at an angle at the eye of 1 f marked impairment over the whole frequency range was demonstrated in ambl anisometropia whereas no changes were found in the intermediary and low freque in strabismus before or following treatment During successful patching trea anisometropic amblyopia an improvement of contrast sensitivity was documented

K Olsson & A Hedin *A better visual acuity test chart?*

The readability of 23 letters were studied in 9 subjects with normal visual acu basis of the result a test chart was conctructed with geometric size progression

G Lennerstrand *Adjustable sutures in strabismus surgery*

The technique of adjustable sutures in squint surgery revised by Jampolsky (Tr *Acad Ophthal Otolaryng 79 704 1975*) has been used in eleven cases of strabism them with incomitancy due to paralysis contracture or scar stricture

After premedication with atropine general anaesthesia was induced with haloth or fenthanyl–N_2O The muscle to be adjusted was secured with 6–0 Vicryl[®] dou was attached to the sclera but the sutures were not tied A slip knot was applied suture ends preventing the muscle to retract beyond the desired position Sclera wa between the original muscle insertion and the limbus

When the patient had fully recovered from anaesthesia which occurred 4 postoperatively eye alignment was tested in different directions of gaze If necess position was adjusted under topical anaesthesia by sliding the slip knot the a amount thereby changing the length of the muscle sutures The suture ends were the sliding knot and trimmed

Suture adjustment was performed postoperatively in nine of the patients 0 muscles were moved A 8 year-old child failed to cooperate but adjustment was m another child 10 years-of age The rest of the patients were between 16 and 66 yea

The possibility of correcting eye position by suture adjustment in the immediate tive period is a valuable supplement in the surgical management of selected strabs It is questionable however whether this precedure should be attempted in children

E Wold & E B Moller *Pregnancy and diabetic retinopathy*

I Gislason A Alm S Stenkula F Wold & P E Wålinder *Cavernous h of the retina*

B Philipson & A Philipson *Postoperative endophthalmitis*

Endophthalmitis is one of the most serious complications following ophthalm The complication has attracted much attention recently because 1) it appears quit the incidence of postoperative endophthalmitis in Sweden has increased over the l increased knowledge of pharmacokinetics of antibiotics has substantially im possibility of successful treatment

e fundamental principle in the treatment of endophthalmitis is to reach therapeuticall iate levels of antibiotic rapidly in the vitreous A great variety of bacterial species, gram ive as well as gram negative can cause endophthalmitis In recent years it has become rent that *Staph epiderm dis* is a frequent cause of endophthalmitis which may appear one ore weeks following ophthalmic surgery As antibiotic therapy must be given immediate- sults from bacteriologic cultures are not at hand Thus a wide bacterial spectrum must vered Suitable antibiotics for initial treatment are gentamicin and penicillin G If the logical agent is suspected to be betalactamase producing staphylococci, gentamicin and izolyl penicillin are a better combination

fferent routes of administration can be used The fastest way to achieve a high level of iotic in the vitreous is to inject the drug into the site of infection i.e intravitreally ever several studies confirm that administration of the antibiotic by inject on subconjunc ly or subtenonially is also highly effective Such administration should alwa s be coupled simultaneous administration of the same antibiotics gi en parenterall

ral administration of these antibiotics is not acceptable as sufficient levels of antibiotics not be reached in the eye Treatment should be supplemented with oral steroids.

case of late postoperative endophthalmitis follo ing cataract surgery has been treated at Eye Clinic at the Karolinska Hospital Culture from the vitreous revealed *Steph rmid s* In this case therapy was given as follows An intra itreal injection of penicill n G) IU was gi en upon admission Simultaneously gentamicin 40 mg and penicillin G 000 IU were injected subtenonially and these injections were repeated on the second third day Systemic therapy was gi en with gentamicin 80 mg intramuscularly t.i.d. and icillin G 5 million IU q 4 h intravenousl Prednisolone 60 mg was gi en daily by mouth oon as culture results were at hand penicillin G was exchanged for cloxacillin 2 g q 4 h. emic antibiotic therapy was given for 12 da s This therapy gave a total remission of the ophthalmitis However a reduced visual acuity remained

Rosengren *The effect of treous currents on d fferent types of etinal holes and t ars.*

he influence of itreous currents on different kinds of retinal holes and tears and their ty to promote detachments is not clearly established.

i model experiments a container with an internal diameter of 28 mm has been used. It placed on a stand which permitted rotation of the container and even attachment to a imp The inner wall of the container was fitted with circular elevations onto which a tic membrane with an aperture (diameter 2 mm) was attached

Then the container is filled with solution of water and suspended particles the plastic nbrane symbolizing the retina will be surrounded b the suspension Consequently en the container is rotated it is possible (with the aid of a slitlamp) to observe currents on h sides of the membrane and passage through the aperture

When the membrane is parallel to the d rection of the current rotation will not cause any sage through the aperture Passage will occur if the membrane makes ngle with the direction of the current. The same thing may also happen if the aperture in membrane is distorted

tructures on the edge of the aperture rising above the membrane cause irregular rents and consequently friction which has to result in traction on the above mentioned ictures In vivo this will cause traction on structures on the edge of a retinal tear and thus d to result in detachment.

The diameter of the aperture is also of greatest importance Diameters of 2 mm 1 mm and

0 5 mm were compared When these are placed n a l ne on a slop ng membrane a through the aperture forms easily when the d ameter is ? mm Th s is more in the case of the 1 mm d ameter and no current passes through the 0.5 mm aperture T into in v vo cond t ons th s means that small ret nal holes hardl perm passage of currents

When elevat on of the ret na is present another factor w ll be n ol ed the mar subret nal flu d This expla ns the qu ck fluctuat ons in the extent of the ele a ion.

Ilmari Rendahl Lecture

Professor Rudolph Witmer (Zurich) *Aet ology of e t*

The cl n cal p cture of ar ous forms of uve t s was described an erio u eti s Fbrinous rit s chron anterior u e t s in ch ldren indocycl s he erochromic c chrom c cycl t s) posterior u e t s (central chor oret n t s chorore nitis juxta serp ginosa and d ssem nata) and pan uve tis (n Bechet s d sease and o her severe f was emphasized that even if each form is eas ly dent f ed th s seldom gi es nf ma the aet ology of the inflammat on The treatment n most cases con ts of steroid lo system cally The use of immunosuppress ve and cytostat c drugs (su h as C lop and Natulan) was considered a valuable alternat ve or complemen to t ea men n cases of chron c cycl t s (n ch ldren) and of pan u e t s

With regard to laboratory find ngs in uve tis t vas po n ed out tha 1) bacter invas on of the u eal tracts is very rare 2) serological tests (for toxopla mos s, tube streptococcal and v ral nfect ons) can never alone g e a def n e proof of the aeti aqueous humour stud es have shown that ant bod es are produced locally in he uvea percentage of pos t ve f nd ngs n uve tis has been very low 4) electronm croscopical of iris b ops es ha e demonstrated mmunologically competent cells n cases of uve HLA system stud es ha e shown a close connection between ank los ng spond l tis in patients w th acute fbrinous rit s and the occurrance of HLA B27 antigens and be Bechet s d sease and HLA B5 ant gens 6) the level of complement components aqueous humour was lowered in anterior u e t s wh le that of C4 and Ig A was elevated

It was concluded that uve t s rema ns a mysterious disease Infect ons may be impor can very rarely be proven Immunological phenomena do occur as shown by serology on the aqueous humour electron m croscopy of r s an d detection of Ig A C3 and C HLA system reflects only the terra n upon wh ch u e t s may e ol e

sor Maurizio Pandolfi M D Malmö Sweden Hemorrhages in Ophthalmology – A Hemostatic Approach Georg Thieme Publishers Stuttgart Price DM 48 – 84 pages 61 figures 17 tables

ocular haemorrhages whether spontaneous traumatic due to eye diseases or following .al intervention will always constitute a problem to ophthalmologists Dr Pandolfi s after an introductory chapter on the mechanism regulating the haemostasis treats of ocular haemorrhages and haemostasis The author groups the intraocular haemorrhages ding to their sites in the eye beginning his description with haemorrhages and fibrinous ation in the anterior segment. Then follows sections concerned with haemorrhages in ous body conjunctiva retina and choroid A fairly large section concentrates on orrhages in relation to ophthalmic surgery and the measures to be taken to avoid pre postoperative haemorrhages e g in patients with a haemostatic defect In an appendix ccount is given of the haemostasis in the presence of retinal thrombo-embolism and etic retinopathy The author attempts in each section to throw some light on the nostatic factors that may influence the pathogenesis and the course of haemorrhages on ye In addition suggestions for prophylaxis and therapy are reviewed

he book gives a clear and easily read account of a very special subject It is highly mmendable

S Fai rschou

sewisch B Perinatal Retinal Haemorrhage Morphology Aetiology and Significance 184 pages 64 figures 13 plates 29 tables Springer Verlag Berlin Heidelberg New York 1979 ISBN 3 540-op167 X Cloth Price DM 58 US Dollar 31 90

s is a valuable comprehensive monograph del ing deeply An extensive literature has n collected and commented on in this book describing well-established morphological ervations histologic studies and last but not least propounding a conclusive view arding the prognosis

ver since the infancy of ophthalmology numerous colleagues have with surprise and even rror noted the high incidence of extensi e retinal haemorrhage of new-born babies (in the iewer s opinion in not less than 50 per cent) This seems particularly surprising compared h analogous extravasations of blood in adults The authors have wondered at the generally y rapid absorption of the blood They have found it difficult to believe that macular edings may be harmless having on the contrary judged them to be responsible for erwise unexplainable amblyopia

The author s series comprises 400 cases subjected to a careful morphological classification stologic examination where such could be carried through study of a relationship if any the course of the delivery and possible medical intervention in this

Follow up examinations have shown such haemorrhage to be harmless In very rare cases ly it may be suspected to be the cause of impa red function

With the publication of Barsewisch s investigations the last word should in the reviewer s inion have been said on this subject

P B andstrup

M *Ruben* Contact Lens Practice – published by Bailliere Tindall London [illegible], available in german

The german edition is published by Gustav Fischer Verlag Stuttgart – [illegible] translated by dr Hans Walter Roth the university clinic in Ulm

The two editions are identical as to the illustrations and very similar in the text [illegible] Walter Roth has exellently translated the many anglo-saxon technical terms into [illegible] which however is hardly of any help to those who are accustomed to these terms

The book provides the practitioner with a basic knowledge of contactlens fitting [illegible] the physiology of the eye and the optics of the contact lens

In every chapter theory practice and interpretation are mixed in a pedagogic [illegible] gives the maximum understanding

[illegible]

Cool S J & Smith E L (Eds) Frontiers in visual science Springer Verlag Berlin 19[illegible] Price US Dollar 41 80

This volume comprises the proceedings of the University of Houston College of [illegible] Dedication Symposium held March 1977 in Houston Texas USA In the preface [illegible] that the intention was "to cover the state of the art knowledge in *all* areas of [illegible] investigation With this magnificent aim fulfilled by 70 papers it will immediate[illegible] understood that a review is not possible There is an overwhelming amount of [illegible] but unfortunately no author or subject index

With its very broad spectrum almost everyone may find something of interest [illegible] is likely to find the whole text The book should be screened by those engaged in [illegible]

[illegible]

Allen F W Essentials of Ophthalmic Optics Oxford Medical Publications Oxford [illegible] Press New York Toronto 1979 127 pages Price Eng pds 1 9[illegible] net

The book Essentials of Ophthalmic Optics is based on a series of lectures given b[illegible] author to ophthalmologists nurses and orthoptists Being a pocket size book of [illegible] pages it is of course not intended as a comprehensive work on ophthalmic op[illegible] author has succeeded in explaining the essential principles in plain and compre[illegible] language References added after each section facilitate further studies by those [illegible] The book is divided into three sections The first headed Pure Optics treats of the [illegible] light refractive index refraction image formation mirror and lenses etc The [illegible] headed Visual Optics deals with vision the eye as an optic instrument obje[illegible] subjective refraction including retinoscopy among others Included in this sect[illegible] passages treating of ophthalmoscopy and heterophoria The third and final [illegible] concerned with fitting of glasses and contact lenses optical aids to partially sigh[illegible] optic principles of the ophthalmological instruments

The book thus covers a wide range of subjects and is recommendable to both o[illegible] mologists orthoptists nurses working within the field of ophthalmology and [illegible] students

S Fr[illegible]

tung von Strukturen und Systemen in der Ophthalmologi R. Sachsenweger ed Nova Acta Leopoldina N F Nv 23ɔ Band 50 Leipzig 1979 188 pages 8ɔ illustrations 18 tables Price M 33 00

publication written in German records the information presented at the Leopoldina ng which took place in Haale (DDR) in the fall of 1977

ː material is divided into 5 basic sections moderated by H Harms and R Sachsenweger ː first section Systeme des Auges comprises information about the functional system ɔpment and biomorphogenesis of the eye The same chapter includes two interesting ːs about retinal structures by H Sautter and about vitreous body structures normal ıgs and pathological changes presented by F J Reutsch

the second chapter the following articles are presented 1 Die Lokalisation von ɔrungen in den System des Sehorgans by E Aulhorn 2 Zur Struktur der oberen ıhn by E Winkelmann and 3 Strabismus concomitans – eine Storung des Bifixations ns by E S Aweussow These three detailed papers include very clear and didactical ıngs

ırphology and circulation of the anterior chamber fluids are presented as a 3rd chapter W Rohen E Barany and H Goldmann

the next chapter diseases of the retina and chorioid are considerated The titles are ıstemgebundene und Systemubergreifende angeborene retinale Storungen by Jaeger ıakulaerkrankungen by H E Henkes and 3 Gefässbedingte Erkrankungen der ıaut by H Goldmann

the final chapter P Niesel discusses the principles of therapy and rehabilitation on latory diseases of the eye The same section includes valuable reflections of E Barany on ɔm therapy

Mackensen writes about Systemerhaltung und Wiederherstellung als therapeutisches ıp aus der Sicht der Oftalmochirurgen

ıally an interesting and actual theme Vitrectomia via pars plana is presented by R.

ıe publication contains much valuable and detailed information and cannot be sum zed briefly

ıere are useful references black and white illustrations as well as very instructive ıngs and tables

ıis book gives an excellent theoretical and practical information and will be of great est to all ophthalmologists

Danuta Marushak

Holl ıch Ophthalmology A short textbook Georg Thieme Publishers Stuttgart 1979 Price DM 29 80

translated edition has like the well known German edition advantages and drawbacks advantages are the small pocket book size the beautiful illustrations and the systematic ːntation of the subject

ıe drawbacks are the many scientifically unfounded treatments e g vitamin A ointment ·phthalmic zoster steroid drops or ointment for optochiasmotic arachnoiditis or iodine ɔsion after abrasion and several misleading references to pages elsewhere in the book probably an error due to the translation

Niels Ehlers

William H. Havener Synopsis of Ophthalmology. The C. V. Mosby Company [illegible] Toronto London 1979. 675 pages, 364 illustrations. Price US Dollars [illegible]

Synopsis of Ophthalmology was written for the purpose of informing general practitioners [illegible] technique of examination, diagnostics and therapy within the field of ophthalmology.

In this book the individual subjects are described with a wealth of details. [illegible] chapter on the diagnostic significance of eye examination in relation to disease [illegible] the body. A passage dealing with the anatomy and physiology of the eye is followed [illegible] comprehensive chapters on case recording and physical examination. The author [illegible] great importance to ophthalmoscopy. Colour pictures of the fundus and numerous [illegible] of ophthalmoscopic findings aid towards giving us an excellent survey and better [illegible]ing of the problems with which the examiner of the internal eye may meet.

The remaining chapters are concerned with ocular signs and symptoms [illegible] systemic diseases, neuro-ophthalmology, proper eye diseases, and ocular trauma. [illegible] chapter is furnished with many good illustrations.

The last chapter, dealing with ocular pharmacology, shows the author's special [illegible] this subject. He gives a careful account of the effects, advantages and disadvantages [illegible] various drugs.

The book ends up with a good index and an extremely useful list of words belonging [illegible] ophthalmological terminology. This fact adds further to its value, also as a reference [illegible]

The book is highly recommendable, also as a textbook for medical students.

S. [illegible]

Frank W. Newell Ophthalmology. Principles and Concepts. The C. V. Mosby Company [illegible] Louis, Toronto, London 1980. 640 pages, 477 ill. Price UK Pds ca. [illegible]

This is a book intended as an introduction to the subject for both students and [illegible] interested in ophthalmology.

In this fourth edition, like in the previous ones, the author has aimed mainly at [illegible] basal knowledge with conversance with ocular manifestations and clinical pictures [illegible] trations on ocular details has been largely avoided out of regard to non-ophthalmologists.

The book comprises four main sections. The first one deals with the relevant [illegible] physiology, biochemistry and pharmacology.

The second section treats of the taking of case histories and with eye examination. [illegible] section is of particular instructive value to students.

The remaining sections are concerned with eye diseases and injuries as well as ocular [illegible] and symptoms in relation to general illness. These sections are likewise well arranged [illegible] well written. Certain details may be criticized, however. Thus for instance [illegible] mentioned as the most common provocative test in simple glaucoma [illegible] hardly deserves. In fact, many workers regard the test as worthless.

This book is about the same size and get up as the previous editions, still has [illegible] pictures. All the illustrations are black and white, which may be a disadvantage [illegible] the cases of the clinical pictures.

Reading of the book has been a pleasure to me, and I can recommend it [illegible] interested in an introduction into the subject.

[illegible]

'', of the ocular adnexa and o bit Ed A Hornblass Mosby St Louis Toronto London 1979 pp 336 608 ill 3 in color US Dollar 69 50

ext of this book in 30 chapters by 93 contributors is based on a conference at the Lenox lospital in New York City in 1977 The first 17 chapters deal with tumors of the ocular :a and the remaining with orbital tumors

phasis is placed on diagnosis and therapy and only sporadically on histopathology nt views on diagnosis and treatment are compiled including ultrasound and CT ing in orbital diagnosis As is customary in proceedings of symposia panel discussions each section are printed The therapeutical methods are thoroughly reviewed and often ated by sketches

: black/white figures however are poor often unsharp and often unillustrative ly because they have been reproduced from color diapositives used during the osium

ny are reproductions from journals The advantage of this book is the presence in one ie and the compilation of diagnosis and therapy of adnexal and orbital tumors It es mainly to ophthalmologists plastic surgeons and radiotherapists

O A Jensen

Perkin an I F Clifford Ro e Optic Neuritis and its Differenual Diagnosis Oxford Medical Publications Oxford New York Toronto Oxford University Press 1979 292 pages Eng pds 20 00 net in UK

uthors present 172 cases of optic neuritis referred to the Royal Medical Ophthalmology in London over a 15 year period

estigative techniques are analysed and compared Symptoms and treatment are dealt n separate chapters and the problems of differential diagnosis are reviewed extensively frequency with which optic neuritis progresses to multiple sclerosis is discussed and the onship between optic neuritis and multiple sclerosis is analysed on the basis of the ture and the authors extensive experience One of several interesting conclusions is that ple sclerosis following optic neuritis pursues a more benign course both in terms of ality and disability than that following other forms of presentation

e book is devoted to demyelination of a tiny part of the central nervous system but to ologists interested in multiple sclerosis and neuroophthalmologists it will be of interest.

Kresten Work

International Society for Contact Lens Research

Notice of 1st Scientific Meeting at Royal College of Surgeons London September 5th 1980

All individuals who have an interest in research and wishing to attend or participate write as soon as possible to Montague Ruben Moorfields Contact Lens Department (Street London EC1 UK

Details regarding membership can also be requested at the same time if required

The International Society for Orbital Disorders

organises the 4th International Symposium on Orbital Disorders on August 31st, September 1st and 2nd 1981 in the International Congrescentrum RAI in Amsterdam

Topics of the congress will be Immunology Radiotherapy Chemotherapy and Surgery of the Orbit

For further information one can write to the secretary general J P A Cillsen, University Eye Hospital Wilhelmina Gasthuis le Helmersstraat 104 1054 EC A Holland

Israel International Symposium on Glaucoma

will take place in Tel Aviv (Israel) september 3 5 1980 Contact Secretariat P O B 16271 Tel Aviv

Annual Conference of the Glaucoma Service of the Wills Eye Hospital

will be held in the new Wills Eye Hospital June 6–7 1980

For further information please contact

Kenneth Benjamin M D c/o Glaucoma Service Wills Eye Hospital
1601 Spring Garden Street Philadelphia Pa 19130 (215) 979 6380

Departments of Paediatrics[1] (Head K H Gustavson)
and Ophthalmology[2] (Head U Hallden) University of Umea Sweden

SPECIFIC CHANGES IN THE FUNDUS TYPICAL FOR THE SJÖGREN LARSSON SYNDROME

An ophthalmological study of 35 patients

BY

S JAGELL[1] W POLLAND[2] and O SANDGREN[2]

All Swedish cases with the Sjogren Larsson syndrome (SLS) i e 35 patients were studied Glistening dots of unknown nature were seen round the fovea These foveal and parafoveal changes seem to be a cardinal sign of SLS together with congenital ichthyosis spastic di tetraplegia and mental deficiency

Key word Sjogren Larsson syndrome – macular changes

jogren Larsson syndrome (SLS) is a genetically determined syndrome with omal recessive inheritance characterized by the three cardinal signs congeni thyosis spastic di/tetraplegia and mental retardation (Sjogren & Larsson Richards 1972 Theile 1974) (Fig 1)

eral authors have noted ophthalmological changes in SLS Sjogren & Larsson) found degeneration of the macula in three of twelve patients The fact that ost marked changes were found in two of the oldest patients made Sjogren & on suspect a slowly progressive macular degeneration However another four r patients in the same ages did not present any changes in their ocular fundi other authors have found macular changes in children with SLS Vissian et al) found a multicoloured glittering fundus in a four months-old girl Gilbert et 968) examined a 2½ year-old boy who had macular lesions in both eyes unding the macular lesions were small glistening dots The electroretinogram ormal Fluorescein fundus angiography revealed an increasing transmission e choroidal vascular pattern Theile (1974) summarized 111 reported patients SLS Different ophthalmologists examined 76 of these patients and they d macular changes in 38 patients and 15 of these showed glistening spots Only

ved December 21st 1979

a few patients were examined by the same ophthalmologist It is well k
patients with ichthyosis may have keratoconjunctivitis blepharitis ecz
corneal opacities (Cordes & Hogan 1939 Hammerstein et al 19 8 Jay
Kuklin et al 1976 Sever et al 1968)

Specific macular changes combined with ichthyosis have not been rep
observations of macular changes of different types in half of the SL
(Theile 1974) could be explained by the assumption that SLS depe
ectodermal disturbance affecting the central nervous system as well a
When one of us (S J) made an investigation of the SLS patients in Swede
an identical type of fundus change in a varying degree in SLS pati
motivated further investigation

The aim of the present study was to find out 1) if glistening d
pathognomonic change in the eyes of SLS patients 2) the age of d
whether 3) there is any correlation between macular changes and
symptoms of a defective central nervous system

Material and Methods

Ophthalmological examinations were performed on all patients with SLS
(20 males and 15 females) The age range was from 1 to 71 years T
examination included ophthalmoscopy slit lamp examination electroe
two cases and photography of the fundus As a control group 14 pa
patients were examined as well as nine mentally retarded patients wi
and ten patients with mental retardation and spastic diplegia None
individuals had SLS

Results

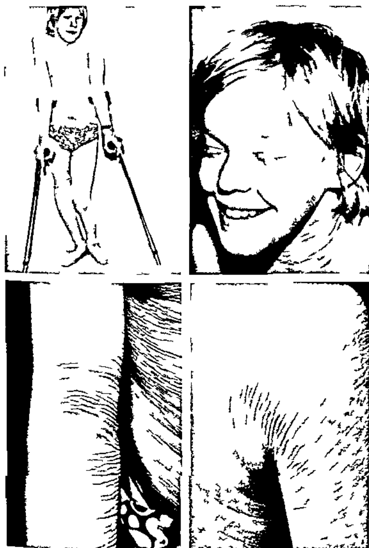
The major ophthalmologic findings of the 35 patients with SLS exam
present authors are summarized in Table I Numbers of patients are a
Jagell 1980 (There are altogether 58 SLS patients known in Swede
numbered from 1 to 58 Only 35 patients were examined in this investi
patients are deceased)

Visual acuity

Visual acuity was difficult to measure because of mental retardatio
estimated in 12 patients to values in most cases between 0 2 to 0 5 with m
about 0 4

ve error

active errors were converted to spherical equivalents Myopia was found in ents of whom three patients had severe myopia with more than or equal to pters Hyperopia was found only in one patient



F g 1

o ol 13 years-old with spastic d plegia l ght mental retardation and general zed chth os s

Table I

Ocular findings in 35 patients with Sjogren Larsson syndrome

Patient number*	Age years	Vision	Refractive error Diopter	Ectropion	Blepharitis	Conjunctivitis	Punctate keratitis	Corneal opacities	Macular glistening dots
11	71	P/P		−	−	−	−	−	
17	63	P/0 1	/+19(op)	+	+	+	+	+	
21	58			−	+	+	+	+	
22	57	0 3 0 3	−1/−1	−	−	+	+	+	+
26	51			−	−	−	+	+	+
28	49			−	+	+		−	
29	45			−	+	−		−	+
30	42	0 2/0 4		−	+	+	+	+	+
31	40			−	+	+		−	+
33	39			+	+	+		−	+
[illegible]	33		−22/−21	−	−	−	−	−	+
35	31	0 2/0 1	−1 5/−1	−	−	−	−	−	+
36	29	0 4/0 5	−0 5/±0	−	+	−	+	+	+
37	26	0 5/0 5	+1 5/+1 5	−	−	−	+	−	+
38	22			−	+	+		−	+
39	21			−	+	+		−	+
40	21	0 [illegible]/0 5	[illegible]	−	−	−	−	−	+
41	[illegible]1		−3 [illegible]/−1 5	−	−	+	+	−	+
[illegible]	[illegible]0	0 4 0 5	−4/−4	−	+	+	−	−	+
[illegible]	18		−15/−15	−	+		+		
[illegible]	[illegible]								

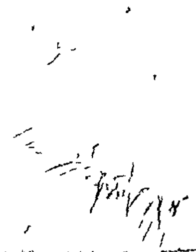
47									
0	11	0 5/0 5	−1 5/−1	−	+	+	+	+	
51	13	0 5 0 5	±0/±0		+	−		−	+
	9	0 5/0 4	C 5/−5	−	−	+	+	−	+
3	3			−	−	+	+	+	+
51	7			−	+	+		+	
55	3			−	−	+	−	−	+
56	5			−	−	+	+	−	+
57	1			−	−	−	+	−	+
9	1			−	−	−	−	−	+
				9/35	19/35	21/35	15/25	11/35	30/30

Number according to Jagell 1980
+ Present
− Absent

Not examined
P Perception
op After cataract extraction

Fig 2





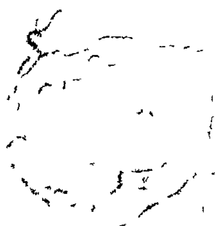




Fig 4

Fig 2 Pat No 40 Eye fundus photograph taken through Goldmann's three-mirror glass

Fig 3 Pat No 21 58 years-old with slight ichthyosis around the eye blepharitis, vitis punctate keratitis and corneal opacities in the lower half of the cornea.

Fig 4 Glistening dots in the fovea of pat No 51

Fig 5 Glistening dots in the fovea of pat No 30

al and conjunctival changes

—l form of ectropion of the lower lids was found in two of the oldest patients aritis and conjunctivitis with redness of the margins of the lids and hyperae onjunctiva were found in most of the patients (Fig 3)

a

n of the patients had corneal changes with equal distribution in both eyes of ent severity from punctate epithelial erosions to grey stromal opacities with larisation (Table I and Fig 3) Stromal engagement was seen more often in the patients The corneal changes were mostly situated in the lower half of the a (Fig 3) The stromal opacities were always located in the anterior half of the a and were in most cases subepithelial

ipatients (Nos 11 and 17) showed dense cataract and lens extraction has been ormed on one eye in one of these patients (No 17) Another patient (No 21) red slight cataract in one eye These three patients are the oldest in our material 71 63 and 58 years respectively

ia

fundus was thoroughly examined in 30 of the patients The examination of the lus was impossible in five of the patients because of cataract or corneal changes our and poor cooperation in one patient All the 30 patients had an identical

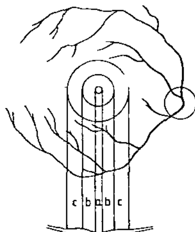


Fig 6

e diagram shows the foveola (a) fovea (b) and parafoveal area (c) with some glistening dots of varying sizes

type of retinal changes around the foveola in the fovea and parafoveal area in Fig 2 4 and 5 These foveolar changes could be described as glittering glistening dots Most dots are seen in the fovea which often has somewhat dots than those seen in the parafoveal area (These areas seen in Fig 6 are according to Hogan 1971) The number of dots vary in different patients about 5 to 50 with about the same number in both eyes in each individual have an irregular shape and are of different size Most often they are from each other but in some of the patients several dots seem to be very each other or confluent One patient (No 40) was examined with Go three mirror contact glass In this wiew the glistening dots looked like irregular bodies with unclear limitation in their periphery like low yellow white tops and greyish slopes situated in the superficial layers of the seen in Fig 2 Nobody in the control group had similar macular changes amount of glistening dots does not seem to be related to age or the mental retardation or spasticity

Other eye findings

Almost all patients had marked photophobia EOG performed in two patients 30 and 51) were normal

Discussion

Ophthalmological examination was difficult to perform because of mental tion and spasticity which are both severe in most individuals with SLS Fur almost all patients had marked photophia

Most patients have a marked ichthyosis over almost the whole body but so slightly involved that they are regarded to be free from any ichthyosis Still some have an obvious others a slight ichthyosis on the forehead involvement of the orbital region

We regard the blepharo-conjunctivitis and punctate keratitis with epithelium to be a symptom of the ectodermal disease SLS-patients ichthyosis have pronounced changes in the superficial part of the photophobia is probably an effect of the punctate keratitis We consider the engagement to be an effect of defective epithelium

Senile lens changes were seen in three patients There seem to be no between cataract and SLS There was an unusually high incidence of study Those patients examined with regard to visual acuity had also values It is however difficult to measure the visual acuity in patients retardation The decreased visual acuity could be secondary to the retardation or secondary to their macular changes

stening dots in the macula have been reported in 15 of 76 patients according ieile (1974) as stated above In our study we found glistening dots in all the SLS nts examined Our investigation included nine of the 13 patients who were nalmologically examined in the study of Sjogren & Larsson (1957) Four of i patients including the three with macular degeneration are deceased Of the ving nine patients three patients have not SLS (Jagell 1980) Of the remaining atients with SLS we were able to examine the fundus of five who all had ning dots Sjogren & Larsson (1957) did not mention glistening dots in their y

ir opinion is that all patients with SLS have glistening dots in their fundi from childhood The changes are probably stationary The reason why other niners do not report glistening dots in all their SLS patients is probably that the iges often are so slight that they are easily overlooked or their significance has een understood The difficulty in examining the patients may also have played e part We did not observe any correlation between the amount of glistening and the severity of spasticity mental retardation ichthyosis or age

istological examination of glistening dots (snailtracks) in the peripheral fundus shown fatty degenerated microglia cells (Daicker 1971) We have not yet been to make any histological examination of glistening dots in the fovea

Acknowledgment

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ie authors thanks are due to B Bergmark M D head of the Department of thalmology Skelleftea for helpful collaboration

References

les F C & Hogan M J (1939) Ocular ichthyosis *Arch Ophthal (Chicago) 22* 590 594
ker B (1972) Zur Kenntnis von Substrat und Bedeutung der sogenannten Schneckenspu n der Retina *Ophthalmologica 165* 360 365
ert W R Smith J L & Nyhan W L (1968) The Sjogren Larsson Syndrome *Arch hthal (Chicago) 80* 308–316
imerstein W & Haensch R (1978) Die Differentialdiagnose der ophthalmologischen efunde bei verschiedenen Formen der Ichthyosis *Fortsch Med 96 Jg 6* 945–251
an M J Alvarado J A & Weddell J E (1971) Histology of the Human Eye p 491 W Saunders Co Philadelphia
ell S (1980) Sjogren Larsson syndrome Clin Genet in preparation
B Blach R K & Wells R S (1968) Ocular manifestations of ichthyosis *Brit J Ophthal 52* 17–926
d n V T Nadelyaeva V M & Trufanova N V (1976) Ocular changes in patients iffering from ichthyosis *Vestnik Oftalm I gn 3* 79–81

Richards B W (1972) Sjogren Larsson syndrome In Vinken P J & B [illegible]
Handbook of Clinical Neurology pp 468–489 North Holland Publ Co [illegible]
Sever R J Frost P & Weinstein G (1968) Eye changes in ichthyosis *JAMA* [illegible]
Sjogren T & Larsson T (1957) Oligophrenia in combination with congenital [illegible]
spastic disorders *Acta psychiat scand 32 Suppl 113* 1–113
Theile U (1974) Sjogren Larsson syndrome Oligophrenia ichthyosis-di [illegible]
Genet 22 91–118
Vissian L Raibaudi R & Vaillaud J C (1971) Syndrome de Sjogren Lars[illegible]
nourisson *Bull Soc franc Derm Syph 78* 500–504

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NATURAL FAT IN EXTERNAL EYE

Vital Stained by Sudan III Powder

BY

M S NORN

Examination of 113 eyes vital stained by Sudan powder revealed that fat on the skin of outer canthus may pass onto the precorneal film (in 68%) and that the most reliable staining is obtained by application on the bulbar conjunctiva below the limbus corneae at 6 o clock

In 41% the precorneal film had stained drops or foam with a tendency towards an increase among pathological cases (infectious conjunctivitis and blepharitis) An increased amount of fat was found in the mucous thread of eyes affected with infectious conjunctivitis and lagophthalmos In a small number of pathological cases fat was also detected on cornea bulbar conjunctiva and inferior fornix

The fatty layer on the lower lid margin was stained more frequently and more intensely than that on the superior

The secretion of the meibomian glands was stained in no more than a scant one half of the glands (on average 44%) independently of age sex site and diagnosis

Key words oil – lipid – fat – sebaceous – Meibomian glands – cornea – conjunctiva – vital staining

...ural fat on conjunctiva and cornea can be detected by Sudan vital staining ...an is water insoluble Sudan can be applied in ointment or oil and used as a vital ...ing (Norn 1963 1977)

...his only gives information about the fate of the ointment resp oil but not ...cerning the natural occuring fat in the external eye For this purpose we can use ...an powder as suggested by Mc Donald in 1969

...he purpose of this paper is 1) to work out an application method for Sudan ...l staining of the external eye 2) to use the method on a clinical material

...eived September 10 1979

Method

Sudan III powder was used (Merck 1380) The powder was introduced [illegible] of a small wooden stick. Only relatively few granules were applied, [illegible] giving no additional intensity of staining Moreover excess dye may [illegible] the surroundings with a consequent risk of staining hands and clothes [illegible] will stand ordinary washing The wooden stick was therefore [illegible] immediately after use

The site of application was found to be critical On application in the [illegible] fornix the granules became enveloped in the mucous thread and [illegible] this on to the skin of the inner canthus In four out of 18 cases [illegible] therefore failed at the first attempt.

When applied on the skin of the outer canthus with *Closed* eye the [illegible] stained structures inside and upon the lid margin in 34% upon but not [illegible] 32% inside alone in 2% while neither lid margin nor eye was vital-stained [illegible]

The method preferred was that of applying dye granules on the [illegible] conjunctiva just below the limbus corneae at 6 o clock This gave [illegible] vital staining in 100% (45 cases) Evidently the granules were not [illegible] mucus until after they had been moved about by blinking and given off [illegible] components present in the external eye including the margins of both lids

In the slit lamp (Haag Streit – magnification × 10–15) it was possible [illegible] lighting (the light beam beside the granule) to distinguish between [illegible] Sudan granules and proper vital staining of fat The granules were black [illegible] the fat had a beautiful red colour Direct lighting gave a red colour to both [illegible] presence of fairly large amounts of fat we saw red drops that were [illegible] than the granules

Proper vital staining was roughly graded from 1 to 5 within the [illegible] regions 3 indicating moderate staining 2 weak 1 minimum 4 fairly [illegible] maximum The values were read 10–20 min after the staining

Material

A total of 113 eyes were subjected to vital staining 45 by application [illegible] limbus at 6 o clock 50 on the skin of the outer canthus with closed [illegible] elsewhere Of these 17 had to be ruled out owing to inadequate [illegible] remaining 96 constituted the clinical material comprising 49 normal [illegible] diseased having the following diagnoses (numbers in parentheses [illegible] conjunctivitis (3) keratitis (6) corneal dystrophy (12) corneal abrasion (1 [illegible] itis or conjunctivitis (7) lagophthalmos (2) postoperatively (9) miscellaneous

Table I

external eye vital stained by Sudan III 49 normal eyes and 47 diseased (vide text) The
dicate the percentage stained in the region concerned (the figures in parentheses represen
the mean staining grade)

	Pre corneal	Cornea	Bulbar conjunctiva	Caruncle	Inferior fornix	Mucous thread	Inferior margin	Superio margin
%	41	0	0	27	0	53	99	86
nean grade	(0 6)	(0)	(0)	(0 4)	0	(0 8)	(2 7)	(? 3)
gical %	60	6	17	21	4	81	100	87
mean grade	(1 ?)	(0 1)	(0 3)	(0 4)	(0 04)	(1 3)	(3 1)	(2 5)

Result

was present in scant amounts only inside the lid margins of normal eyes ssed by Sudan vital staining Precorneally we saw fine drops or foam formation he caruncle a red ring was observed round a small number of ciliary roots cating presence of fat in the hair follicle Odd scattered fat drops occurred in mucous thread of the inferior fornix (Table I) In the pathological cases corneal fat tended to be more frequent and present in larger amounts than in mal eyes (difference not significant) particularly so in cases of infectious junctivitis blepharitis and after operation often occurring in lagoons Fat ched to the cornea was seen in cases with Dellen and corneal abrasion

n some pathological cases (lagophthalmos round a Bitot s spot etc) fat was iced on the bulbar conjunctiva and in the inferior fornix This was never seen in mal eyes Stained fat was never observed on the plica semilunaris the tarsus nor Marx line The mucous thread of diseased eyes was more often than that of mal eyes seen to contain fat (81% against 53% $P < 0.02$ Student s t test) This particularly so in cases of infectious conjunctivitis and lagophthalmos

The *lid margin* naturally presented intense diffuse staining of the fatty layer rply demarcated from the lacrimal river (= tear prism) and thus also from rx line Vital staining with Sudan and lissamine green showed this beautifully A oad band of stained fat was formed within which a green Marx line was seen e two dyes adjoined without ever mixing (Fig 1)

The boundary line was noticed to be irregular in several cases unlike the nditions in rabbits where the line is regular festoon shaped

Fat was observed more frequently and in larger amounts on the lower lid margin in on the upper (Table I $P < 0.05$) The location depended on the method of



Fig 1

Natural fat stained by Sudan powder and Marx line stained by lissamin green. [illegible] outlets of the Meibomian glands are stained at the lateral part of the eye lid margin.

application The staining was most often located laterally when the dye was [illegible] on the skin of the outer canthus (92%) and most often medially on [illegible] below the corneal limbus at 6 o clock (87%) However external application [illegible] medially (8%) while in 9% application at 6 o clock stained the margin laterally [illegible]

Table II

Sudan vital staining of secretion at the outlets of Meibomian glands in per cent of the number of possible glands An average of 44% were stained in the individual subject

	Upper lid	Lower lid	Number of glands	Number of eyes
Normal	31	46	489	[illegible]
Pathological	45	51	601	[illegible]

outlits of the Meibomian glands were seen at the line where the fat stained
n adjoined Marx line The row of glands may be so irregular that some open
thin Marx line As might be expected the fat present at the outlet was in
l cases stained intensely red However in 56% of the glands the outlets had
ned unstained even though the environments were stained Evidently the
was in such cases covered by a fat free membrane Staining of the outlet of
eibomian gland was independent of age and sex No significant difference was
between upper and lower lids nor between normal and diseased eyes (Table II)
on stained Meibomian gland may become stained after expression A stained
may burst and send a cloud of fat into the precorneal film A Meibomian
in the aqueous phase (Marx line) may show prominence of fat while at the
ime the neighbouring gland in the lipid phase may not be stained by Sudan

Discussion

been shown previously that ointment applied on the skin of the outer canthus
the eye is closed may be transferred to the precorneal film by blinking and be
t by the mucous thread in the inferior fornix It will then pass with this on the
f the inner canthus (Norn 1977)

ng Sudan powder it was shown in the present study that natural sebum from
in may pass the same route This affords evidence to suggest that the
ficial fatty layer of the precorneal film consists of sebum from the skin plus fat
the Meibomian glands The latter are presumed to be secretorily active at
als only more than half of them being covered by a membrane

ve previously subjected mucous threads removed from the inferior fornix to
scopical examination for fat (Norn 1963) As also noticed in the present
al the amount seemed to have increased in cases of lagophthalmos The even
layer of the precorneal film is so thin that it will not be detectable by Sudan
ng The layer can however be measured semi-quantitatively by interference
in the slit lamp (Norn 1979) It is about 100 nm thick in normal eyes – thicker
pharitis and infectious conjunctivitis This is in agreement with the results of
resent investigation

Acknowledgment

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References

Mc Donald J E (1969) Surface phenomena of the tear film *Amer J Ophth* [illegible]

Norn M S (1963) Fatty substancies on conjunctiva *Acta ophthal (Kbh)* [illegible]

Norn M S (1977) Eye Ointments Application elimination and protective action [illegible] *Digest 39*

Norn M S (1979) Semiquantitative interference study of fatty layer of precorneal [illegible] *ophthal (Kbh) 57* 766~774

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CLINICAL ASSESSMENT OF COLOUR DISCRIMINATION IN SENILE MACULAR DEGENERATION

BY

K J BOWMAN

The colour discrimination of 15 subjects manifesting senile macular degeneration was investigated over a wide range of illuminances using the Farnsworth Munsell 100-Hue test and Panel D 15 Ten subjects of similar ages with normal colour vision were investigated concurrently to provide a control group Colour discrimination was shown to deteriorate with decreasing illuminance this being more marked for the subjects with senile macular degeneration than for the normal subjects It is demonstrated that the FM100 is the preferred test for assessment of colour discrimination loss in senile macular degeneration with early visual acuity loss The Panel D-15 is more useful as acuity loss becomes more marked

Key words senile macular degeneration – colour vision – eye disease – age – colour discrimination

course of senile macular degeneration (SMD) can be monitored by the sment and measurement of a number of visual functions Visual acuity and ır discrimination are obvious and simple functions to assess Central visual s can be plotted but the procedures are less simple if meaningful results are to btained

hile visual acuity is the traditional and conventional means of assessing visual unction monitoring colour vision can be a useful addition tool in the manage

ived October 2nd 1979

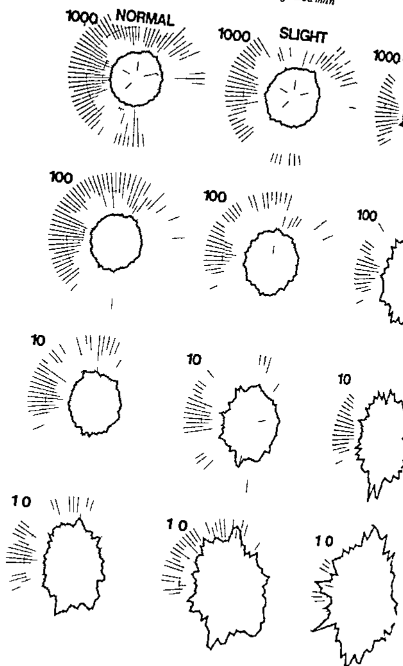


Fig 1

roup mean FM100 patterns for the normal control slight and defin e SVD gr four illuminance levels (1000 100 10 and 1 0 lux)

of senile macular degeneration (Perdriel et al 1970) This may be particularly the early stages of the disease process where acuity changes are absent or ial or where the rate of acuity deterioration is slow and difficult to assess itely

Farnsworth Munsell 100-Hue test (Farnsworth 1943 1957) is admirably to the clinical assessment of colour discrimination although when functional loss is gross and colour discrimination poor meaningful results are more ılt to obtain (Chisholm 1969) Recent advances in the automation of the ıg and plotting of the FM100 results (Taylor 1978 Donaldson et al 1978) ld provide an impetus for its more widespread use in larger clinics whereas to ts use has generally been restricted to research departments

dyschromatopsia accompanying senile macular degeneration is generally nized as a blue yellow or tritan defect (Cox 1961 Francois & Verriest 1961) ugh non specific defects have been reported (Campbell & Rittler 1972 ers 1972) These investigations have usually been conducted at various levels ıminance and age-matched control groups have not been studied concurrently e two factors are important since FM100 performance in particular has been onstrated to be both age and illuminance dependent (Verriest et al 1962 iest et al 1963 Cornu & Harlay 1969)

is present study examines the colour discrimination of subjects manifesting macular degeneration the effect of illuminance on discrimination and pares their performance with that of an age matched normal control group

Materials and Methods

ẞen subjects (mean age 66 5 years) with senile macular degeneration and an matched control group of 10 subjects (mean age 64 0 years) with normal colour n and manifesting no ocular pathology were studied Subjects with medial ities were excluded from participation in order to equalise selective absorption ts between groups and also to ensure visual acuity changes were due solely to senile macular degeneration The 15 subjects with senile macular degeneration divided into two groups designated slight (8 subjects) and definite (7 ects) solely according to visual acuity measurements using the acuity chart of ey & Lovie (1976) The criteria for classification were Slight 6/6 – 6/12 finite < 6/12 – 6/30 each group representing four acuity lines on this chart a se of 0 4 log units of minimum angle of resolution

ollowing a familiarization trial at 1000 lux to reduce learning effects the FM100 performed twice by each subject in a counterbalanced ABBA sequence at each

the most consistent tritan patterns (Fig 5) whereas these traces appear at levels of illuminance for the slight group Since the Panel D-15 is administered at levels of at least 100 lux it is evident that the detection of defect in SMD by this test is doubtful until acuity is reduced below app 6/12 Until this reduction in acuity is reached the FM100 is the prefe detect the loss of colour discrimination This relationship between visual Panel D 15 performance in senile macular degeneration has previously by *Helve & Krause (1972)*

Discussion

Older subjects with normal colour vision suffer marked loss of discr surface colours in conditions of low ambient illuminance Subjects senile macular degeneration suffer more marked loss of discriminatio *related to the severity of the acuity loss*

The FM100 would appear most useful for the clinical assessment discrimination with early visual acuity loss As this acuity loss bec substantial and FM100 results less definitive the Panel D 15 provides a reliable technique

References

Bailey I L & Lovie J E (1976) New design principle for visual acuity letter ch *Optom 53* 740–745

Bowman K J (1973) The Farnsworth Dichotomous test – The Panel D-15 ... 13–24

Campbell C J & Rittler M C (1972) Color vision in retinal patholog degeneration *Mod Probl Ophthal (Basel) 11* 98–105

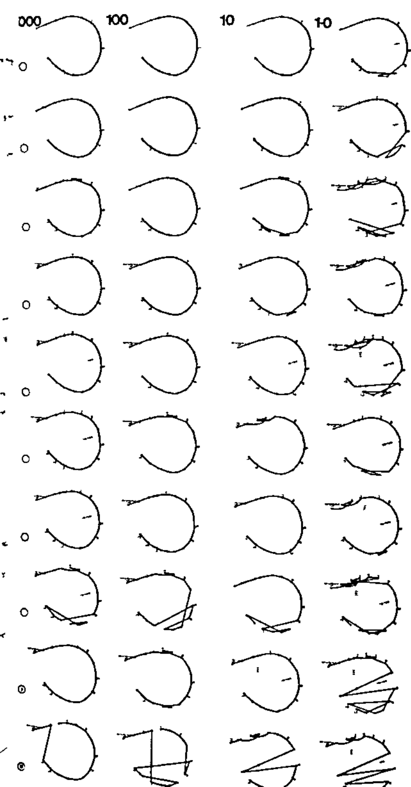
Chisholm I A (1969) An evaluation of the Farnsworth Munsell 100-Hue test as in the investigation and management of ocular neurological deficit *Trans* ... *89* 243–250

Cornu L & Harlay F (1969) Modification de la discrimination chromatique en l'eclairement *Vision Res* 9 1273–1287

Cox J (1961) Colour vision defects acquired in diseases of the eye *Brit J* ... *3–32*

Fig 3

Panel D 15 patterns for the ten normal control subjects at each of the four il...


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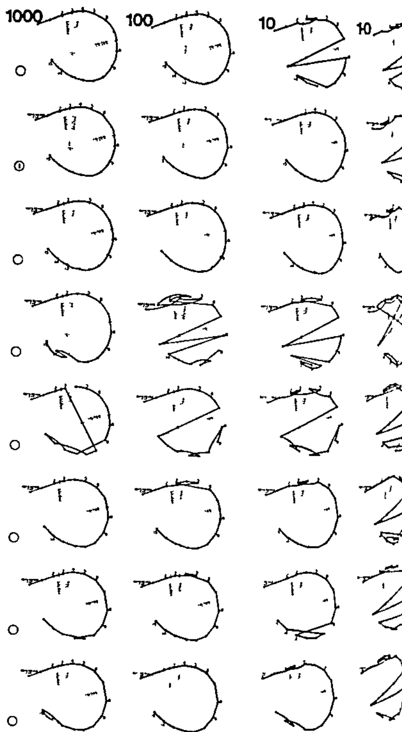


Fig 4
Panel D 15 patterns for the eight slight SMD group subjects at each of the f[illegible] levels

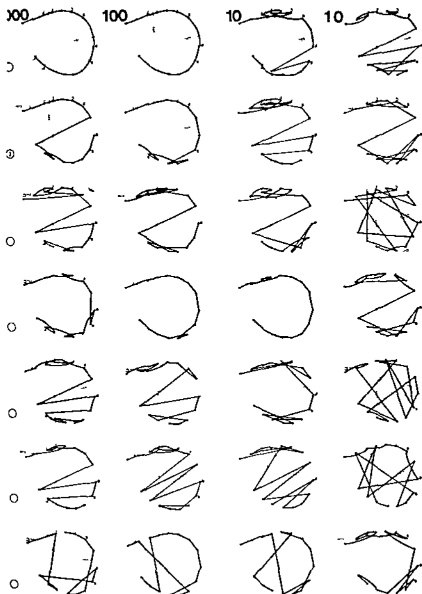


Fig 5

nel D 15 patterns for the se en defin te SMD group subjects at each of the four illuminance levels

Donaldson G B Pritty D W & Bryan W (1978) Progress in the instrume[illegible] Farnsworth's 100-Hue test *Mod Probl Ophthal (Basel) 19* 155–158

Farnsworth D (1943) The Farnsworth Munsell 100 Hue test and Dichotomous test [illegible] vision *J Opt Soc Amer 33* 568–578

Farnsworth D (1947) *The Farnsworth Dichotomous Test for Color Blindness Panel D-15* [illegible] Psychol Corporation New York

Farnsworth D (1957) *The Farnsworth Munsell 100 Hue Test for the exam[illegible] Discrimination* Manual Munsell Color Co Inc Baltimore

Francois J & Verriest G (1961) On acquired deficiency of colour vision [illegible] 201–219

Helve J & Krause U (1972) The influence of age on performance in the Panel D-1[illegible] vision test *Acta ophthal (Kbh) 50* 896–900

Lakowski R (1966) A critical valuation of colour vision tests *Brit J physiol Opt* [illegible]

Perdriel G Chevaleraud J Delpuget J & Bourgeois H (1970) L'exploration [illegible] dans les degenerescences maculaires seniles *Bull Soc franc Ophtal 8*[illegible] 4[illegible]

Pinckers A (1972) An analysis of colour vision in 314 patients *Mod Probl Oph*[illegible] 94–97

Taylor W O C (1978) Clinical experience of electronic calculation and automatic p[illegible] Farnsworth's 100 Hue test *Mod Probl Ophthal (Basel) 19* 150–154

Verriest G Buyssens A & Vanderdonck R (1963) Etude quantitative de l'effet qu[illegible] les resultats de quelques tests de la discrimination chromatique une diminu[illegible] selective du niveau d'un eclairage C *Rev Opt 42* 105–119

Verriest G Vandevyvere R & Vanderdonck R (1962) Nouvelles recherches se [illegible] l'influence du sexe et de l'age sur la discrimination chromatique ainsi qu'a la s[illegible] pratique des resultats du test 100 Hue de Farnsworth Munsell *Rev Opt 41* [illegible]

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FLUORESCEIN ANGIOGRAPHY IN DIABETIC CHILDREN

BY

KIRSTEN STARUP[1] HANS WALTHER LARSEN[1] BERNHARD ENK[2]
and SVEIN VESTERMARK[3]

In 63 diabetic children aged 10–14 years with normal ophthalmoscopy fluorescein angiography revealed slight diabetic retinopathy in maximally three aged 12–14 years These findings are discussed in relation to the controversial results published in a few other fluorescein angiographic studies on diabetic children

It is concluded that normal ophthalmoscopy does not exclude the presence of diabetic retinopathy and that fluorescein angiography is a valuable method in the early diagnosis of diabetic retinopathy

Key words fluorescein angiography – diabetic retinopathy – diabetic children – diabetes mellitus

ntil about 1960 the development of ocular fundus changes could be observed and llowed by ophthalmoscopy and fundus photography only Since the introduction fluorescein angiography by Novotny & Alvis (1961) more information has been tained on the retinal circulation and the development of pathologic fundus anges in various diseases among others in diabetes

Until this study started only a few fluorescein angiographic studies had been iblished on fundus changes in juvenile diabetes

ceived October 22nd 1979

Barta et al (1972) and Brooser et al (1975) found a remarkable [illegible] retinopathy in diabetics under the age of 15 years

Toussaint & Dorchy (1974) in their study of juvenile diabetics did not [illegible] retinopathy before the age of 15 years

The results of Barta et al (1972) and Brooser et al (1975) are in striking [illegible] to the general concept that diabetic retinopathy seldom occurs before [illegible] Therefore we felt that further fluorescein angiographic investigations [illegible] quired and started a fluorescein angiographic study on diabetic children [illegible]

Material and Methods

The study included 63 diabetic children aged from 10 to 14 years Thirty [illegible] girls and 31 were boys All were randomly selected among outpatients [illegible] Department of Paediatrics Glostrup Hospital and the Steno Memorial [illegible] Gentofte The investigations were performed after obtaining informed [illegible] both the children and their parents

Twenty seven of the children had a family history of diabetes Two [illegible] children were siblings but not twins

The ages of the children at the time of the ophthalmologic examination [illegible] from 10 to 14 years with an average of 12 years The duration of diabetes [illegible] from one month to 13 years average 4 6 years

All patients were treated with diet and highly purified porcine insulin, [illegible] (65%) of them received insulin twice a day The dose of insulin ranged from [illegible] 1 3 IU/kg (average 0 74 IU/kg)

All patients were controlled in the diabetic clinics at regular intervals of [illegible] months

During the observation period which in most instances was from the [illegible] diagnosis of the diabetes 12 of the children had been hospitalized. Seven [illegible] ketoacidosis 3 once for diabetic coma and 2 twice and nine times respectively [illegible] severe hypoglycaemia

Body weight and height were compared with ideal body weight and height [illegible] Danish normal material (Andersen et al 1974) and showed on the average [illegible] values

Glycosuria was measured in fractionated urine collections almost daily [illegible] and in 24 hour urine at the control visits

Status of regulation (Table I) was grouped into 3 categories good [illegible] and poor The grouping was based on accurate notes in the records on the [illegible] of admissions necessary for regulation including episodes of ketoacidosis [illegible]

Table I
Estima ed status of regulation

Regulation group	Number of patients	
	Total (n = 63)	With retinopathy
Good	27	2
Moderate	18	1
Poor	18	0

na or hypoglycaemia and the values of blood glucose glycosuria ketonuria and ght and weight during the observation period

None of the children had clinically overt late diabetic complications or presented ner general diseases and none of the children received any other drugs than ulin

The ophthalmologic examinations included refraction and corrected visual uity slit lamp examination ophthalmoscopy fundus photography and fluores in angiography The fluorescein angiograms were evaluated independently by o ophthalmologists

The photographic records were made following maximal dilation using tropi mide (Mydriacyl®) 1% and cyclopentholate (Cyclogyl®) 1%

Colour fundus photographs were taken with the Topcon fundus camera on odachrome 25

Retinal fluorescein angiography was performed on the posterior pole of the right e in each child as the early sequence study area in the initial 10–120 seconds ter photographs covering an area of at least 30 around the disc were taken

Table II
Diabetic children with abnormal fluorescein angiography

Age (in years)	Sex	Diabetes in the family	Duration of diabetes (in years)	Number of microaneurysms
14	male	+	13	1
19	male	–	7	1
14	male		6	Several

following the main series Additional photographs of the posterior pole [illegible] 10 min and 30 min after the injection of fluorescein The dose of [illegible] fluorescein (in a 10% solution) was based on body weight at about 10 [illegible] injected as a bolus into a cubital vein The angiograms were taken with the fundus camera equipped with standard filters No complications were [illegible] *relation to the fluorescein angiographies apart from slight nausea in four [illegible]*

Results

In all children ophthalmoscopy and fundus photography were normal [illegible] children showed pathologic lens changes

The fluorescein angiograms were normal in 60 cases Three [illegible] abnormalities (Table II) Two had changes which were interpreted as [illegible] microaneurysms and one had some microaneurysms and dilated leaky [illegible] capillaries (Fig 1) None showed alterations in the macular pigmentation.

All of the three children with retinal changes were considered to be in [illegible] state of regulation although one showed retardation of growth

Discussion

The incidence of diabetic retinopathy rises slowly during the first five [illegible] diabetes and more slowly in the younger age group than in the older age [illegible] juvenile diabetes the general concept based on ophthalmoscopy has been [illegible] retinopathy rarely occurs before the age of 16 years no matter how long the [illegible] has been present (Larsen 1960)

As fluorescein angiography often reveals more microaneurysms than can be [illegible] ophthalmoscopically (Scott et al 1964) this general concept might have [illegible] changed somewhat

In a fluorescein angiographic study Barta et al (1972) presented a [illegible] remarkable incidence of microaneurysms in juvenile diabetics

The results were based on a material of 111 diabetics 49 boys and 6[illegible] whom diabetes was diagnosed before the age of 14 years All patients [illegible] normal ophthalmoscopy but 61 (55%) presented microaneurysms on fluore[illegible] angiography Eighteen out of 40 (45%) presenting microaneurysms were [illegible] years old and 43 out of 71 (61%) were 15 years old or more The incide[illegible]

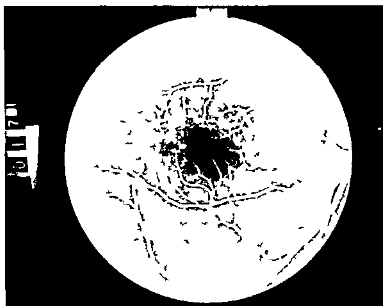


Fig 1

"n patient No 3 Fluorescein angiogram (17 seconds after injection of dye) showing some
oaneurysms and dilated leaking retinal capillaries temporal and above the fovea centralis

betic retinopathy rose not only in relation to the age of the child but also in ation to the duration of diabetes while no significant correlation was found ween the control of diabetes and the occurrence of retinopathy

In another fluorescein angiographic study on 161 diabetic children with normal hthalmoscopy Brooser et al (1975) found microaneurysms in 42% in the age oup 3–10 years 59% in the age group 11–15 years and 86% in the age group –18 years With a duration of diabetes from 0–5 years 50% showed diabetic tinopathy with a duration from 6–10 years the incidence rose to 84% and in ses with a duration from 11–18 years the incidence was 74%

Toussaint & Dorchy (1974) and Toussaint et al (1976) examined 30 diabetics ed 9–32 years Diabetes was diagnosed before the age of 15 years Fluorescein giography revealed no retinopathy in the age group under 15 years

In another fluorescein angiographic study on 87 diabetics with an onset of abetes before the age of 14 years Dorchy et al (1977) found five cases (11%) of etinopathy among 45 children under 15 years of age They also found that the uration of diabetes and a poor control augmented the incidence of retinopathy onsiderably

Malone et al (1977) published a fluorescein angiographic study on 1... aging from 5–18 years Diabetic retinopathy was demonstrated by ... graphy in 22 of which 12 were aged 8 to 15 years Fluorescein angio... revealed vascular defects in 74% of the children who showed no abnorm... the retinal colour photographs

In the present material evidence of diabetic retinopathy was found ... three (5%) out of 63 children At present variations in the normal fluo... angiogram have not been investigated It is therefore not known whether microaneurysms can be present in normals These three had had diabetes ... and 13 years (14% of the patients with a duration of diabetes more than ... They were 12–14 years old and were considered to be in reasonable ... regulation although one showed retardation of growth However they ... differ from the rest of the material

These findings are in agreement with the findings of Toussaint et al (19...) and Dorchy et al (1977) but in striking contrast to the findings of Bar... (1972) Brooser et al (1975) and Malone et al (1977)

The mechanism of development of diabetic microangiopathy and retinop... still not fully understood although much research has been done and ... hypotheses have been put forward Besides basic factors such as hyper... metabolic changes in the tissues the status of regulation diet insulin, pube... genetics have been postulated as factors influencing the development of d... retinopathy

Can differences in these parameters explain the discrepancy in the ... obtained?

Barta & Molnar (1970) found a definite tendency to retinopathy in ... diabetics when retardation in growth was present In our material howe... one of the three presenting retinopathy on fluorescein angiography ... retardation in growth

Barta et al (1972) and Malone et al (1977) did not find any correlation b... the degree of control and the occurrence of diabetic retinopathy while D... al (1977) found such a close relationship However the degree of control or ... regulation are not adequately specified

Differences in diet or insulin could be factors which might influence ... development of retinopathy Job et al (1978) split up the daily insulin ... showed that this regimen was effective in improving the diabetes regula... delaying retinal changes Specified informations on diet purification and ... tration of insulin are however lacking in most materials

Barta et al (1972) Brooser et al (1975) and Malone et al (1977) f... considerable number of children with retinopathy before the age of 10 years ... present material none of those presenting retinopathy were pubescent

enet c influence on the development of retinopathy independent of the ol c changes in diabetes was suggested by Brooser et al (1975) because of the nt occurrence of m croaneurysms soon after the onset of d abetes The of the present investigation however cannot support this theory s nce ce of retinopathy d d not occur in any case before d abetes had been present east s x years

ie of the discrepancies in results obta ned from these fluoresce n angio-c stud es may be due not only to d fferences in the materials etc but also to a ent interpretat on of the fluoresce n angiograms Attent on should be drawn fact that defects in the p gment ep thel um can be mposs ble to distinguish m croaneurysms unless a comprehensive sequence of photographs is available arefully stud ed

an howe er be concluded that normal ophthalmoscopy does not exclude the nce of diabet c retinopathy and that fluoresce n angiography s a valuable od in the early d agnosis of d abetic retinopathy

s n tial study will be followed up on the same material at two-year intervals to sh the natural history of the d sease and to ensure the correctness of the oretat on of our results

Acknowledgments

au hors w h to express the r gratitude to Kirsten Dyrløv Departmen of Paediatrics rup Hosp tal for outstand ng techn cal ass stance

References

ersen E Ande sen H Hu ch ngs B Pe tersen B Rosen J Thamdrup E W chmann & Nyholm M (1974) He ghts and we ghts n Dan h school ch ldren n 1971 1972 sk *Læg 136* 2796 2809

a L Brooser C & Molnar M (1972) Diagnos c mportance of fluoresce n angiography nfantile diabe es *A ta Diabet Lat 9* 290 298

a L & Molnar M (1970) Uber den Ze punk des Auf n ts der Retinopa h e be m nd hen Diabetes *H l Ped A ta 25* 249 247

ser G Barta L Anda L & Molnar M (1975) Fruhdiagnose der M kroangiopa h e be nd hem Diabetes *Kl n Mbl Augenheilk 166* 233 236

chy H Toussa nt D Devroede M Ernould Ch & Loeb H (197) D agnos c de la nopath e d abe que nfantile pa angiograph e fluo esce n que *Nouvel P e Med 6* 45 317

Job D Eschwege E. Guyot Argenton C Aubry J P &Tchobroutsky G (multiple daily insulin injections on the course of diabetic retinopathy Diabe
Larsen H W (1960) Diabetic retinopathy Acta ophthal Suppl 60
Malone J I Van Cader T C & Edwards W C (1977) Diabetic vascular cha *Diabetes* 26 673–679
Novotny H R & Alvis D L (1961) A method of photographing fluorescence in blood in the human retina *Circulation* 24 82–86
Scott D J Dollery C T Hill D W Hodge J V & Fraser R (1964) Fluoresce diabetic retinopathy *Brit Med J* 1 811–814
Toussaint D & Dorchy H (1974) Exploration angiofluorescéinique de la diabétique infantile *Bull Soc belge Ophtal* 168 783–800
Toussaint D Quaetaert M Dorchy H & Loeb H (19 6) Early diagnosis of juvenile diabetes by fluorescein angiography *Acta Paediatr belg* 29 1 18

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FLUORESCEIN ANGIOGRAPHY IN DIABETIC CHILDREN

a Follow up

BY

KIM FROST LARSEN and KIRSTEN STARUP

The present study is a fluorescein angiographic follow up of 60 diabetic children (aged 12–16 years)
At the follow up with two-thirds of the children in pubescence fluorescein angiography revealed diabetic retinopathy in 10 (17%) of the children.
The results indicate puberty as a probable determining factor influencing the onset of the diabetic retinopathy

Key words fluorescein angiography – diabetic retinopathy – diabetic children – diabetes mellitus

means of fluorescein angiography microvascular changes usually can be onstrated in diabetes mellitus before they are opthalmoscopically visible and eover in cases with ophthalmoscopically visible microaneurysms fluorescein iography usually shows a larger number of microaneurysms than can be seen ithalmoscopically Fluorescein angiography therefore provides a more reliable hod of detecting the initial signs of diabetic retinopathy and assessing the valence of this condition among diabetic children Until the present fluorescein iographic study was started in 1975 such studies on fundus changes in juvenile

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diabetics as had been published had given only few and rather con[illegible] (Barta et al 1972 Brooser et al 1975 Toussaint & Dorchy 1974)

These obviously conflicting results did not seem to be due to differen[illegible] the criteria for selecting the patients or the metabolic state The presen[illegible] angiographic investigation designed as a long term study was started w[illegible] of contributing to a clarification of the problem of the debut and pr[illegible] diabetic retinopathy in childhood and the possible influence of pube[illegible] onset and development of the disease The results of the initial inves[illegible] been presented in an earlier article (Starup et al 1980) This paper pre[illegible] results of the first follow up carried out in the autumn of 1977

Material and Methods

The initial study included 63 children with insulin-dependent diabetes me[illegible] Three of these were lost to follow up one had moved abroad one had refused e[illegible] on religious grounds and one had died from leukaemia At the follow up girls and b[illegible] equally represented The ages of the children and the duration of IDDM at the tim[illegible] initial examination and the follow up are shown in Table I In the period betwe[illegible] examinations the percentage of children receiving insulin twice a day had increa[illegible] 65% to 87% and the daily dose of insulin had increased from an average of [illegible] (range 0 20–1 30 IU/kg) to 0 96 IU/kg (range 0 30–1 60 IU/kg) (Table II [illegible] performance of the initial study two years ago two children had been hospitalize[illegible] episodes of severe hypoglycaemia but none of the patients had had ketoacidos[illegible] of long term metabolic control was based on body weight and linear growth of the [illegible] and showed on average normal values None of the children had clinically overt la[illegible] complications or presented general diseases and none received any drugs other [illegible] At the preliminary examination none of the children showed signs of puberty [illegible] follow up 65% had grown into puberty The study was performed after obtaining [illegible] consent of both the children and the parents

Table I
Age and duration of diabetes at the two examinations

Examination	Number of cases	Age (in years) $\bar{x} \pm$ SEM	Duration of diabetes (in years) $\bar{x} \pm$ SEM
Preliminary	63	12 ± 0 9	4 6 ± 0 4
Follow up two years later	60	14 ± 0 2	6 6 ± 0 4

Table II
Dose and administration of insulin at the two examinations

Examination	Daily dose of insulin (in IU/kg) $\bar{x} \pm$ SEM	Percentage of children receiving insulin twice a day
Preliminary	0 74 ± 0 08	67%
Follow up two years later	0 96 ± 0 09	87%

ophthalmological examinations included refraction and corrected visual acuity sl t examination ophthalmoscopy fundus photography fluorescein angiography and netry The technique was the same as in the initial study but fluorescein angiograms in esent study were taken with a Kowa wide angle (42°) fundus camera model RC W xed with Kodak W 15 and W 56 interference filters

ee of the children had mild and transient nausea immediately after the injection of scein apart from this no side effects were recorded All angiograms from each patient issessed independently by both authors and the readings were further confirmed by an endent observer (Professor Hans-Walther Larsen) To rule out artifacts a lesion had to r at the same site in at least two photographs

tometry a simple test for initial dark adaptation was recorded by means of the ration nyctometer (Registrier Nyktometer) made by VEB Carl Zeiss (Jena DDR) metry was included in this study because of the probable predicti e and prognostic of this test in diabetic retinopathy (Frost Larsen et al 1980)

ier s exact test was utilized in the statistical analysis of the data

Results

ported in the initial study maximally three of the children presented diabetic opathy

the present study five of the children showed vascular abnormalities as single few red dots on ophthalmoscopy These fundus changes could all be seen on colour retinal photographs and in addition, colour fundus photographs iled red dots in a further three children In six of these eight children the tic fundus changes were bilateral while the remaining two showed single dots e right eye only None showed any hard exudates or alterations in the macular ientation

Table III
Age and duration of diabetes at the follow up

Diagnostic group	Number	Age (in years) $\bar{x} \pm SEM$	Duration of diabetes (in years) $\bar{x} \pm SEM$
Total material	60	14 2 ± 0 2	6 6 ± 0 4
Retinopathy	10	15 2 ± 0 1	7 6 ± 1 3
No retinopathy	50	14 3 ± 0 2	6 4 ± 0 4

The fluorescein angiography revealed diabetic retinopathy in 10 childr[illegible]
17% of the total material including all of the eight children in whom [illegible]
was demonstrated on the colour retinal photographs The remain[illegible]
shown normal fundi on both ophthalmoscopy and colour fundus photo[illegible]
was obvious that the fluorescein angiograms demonstrated a greater de[illegible]
pathological fundus changes than could be noted on the colour photograph[illegible]
of the children had more than six microaneurysms in each eye and th[illegible]
leaking retinal capillaries None showed non perfused areas or neovascular[illegible]

The children with diabetic retinopathy were older and had a longer dura[illegible]
diabetes than the children without retinopathy (Table III) but these di[illegible]
were not statistically significant

Ninety per cent of the children with retinopathy had grown into puber[illegible]
only 62% of the children without retinopathy were in puberty and this d[illegible]
was statistically significant ($P < 0\ 05$ (Table IV))

The average daily dose of insulin was slightly but not statistically sign[illegible]
higher among the children with diabetic retinopathy compared to the [illegible]
without retinopathy Furthermore in all children showing retinopathy a[illegible]

Table IV
Distribution of cases with retinopathy in relation to puberty

Diagnostic group	Pubescent	Non pubescent
Retinopathy	90%	10%
No retinopathy	62%	38%

Table V
Dose and administration of insulin at the follow up

Examination	Daily dose of insulin (in IU/kg) $\bar{x} \pm$ SEM	Percentage of children receiving insulin twice a day
Total material	0 96 ± 0 09	87%
Retinopathy	1 05 ± 0 12	100%
No retinopathy	0 94 ± 0 09	84%

insulin was necessary in two daily doses while some of the children without athy received insulin only once a day (Table V)

two of the children presenting diabetic retinopathy had evidence of growth as an indicator of poor diabetic control while the remaining eight children t differ from the rest of the material in this respect Only three of the n presenting diabetic retinopathy had a relative with diabetes In the course ut two years the incidence of diabetic retinopathy in the children under had increased from 5% to 17%

ll 60 children nyctometry showed normal values The cooperation between ers and patients was excellent throughout the study

Discussion

iled discussion concerning the discrepant results of previous fluorescein raphic studies in diabetic children has been presented in the initial study p et al 1980)

results of our follow up study demonstrate a significant increase in the nce of retinopathy in this study group in the course of about two years In the children who had diabetic retinopathy at the preliminary investigation ineurysms were still present but at different sites in the retina Our results istrate a statistically significant difference ($P < 0.05$) in the occurrence of ic retinopathy between the groups of pubescent and non pubescent children e other hand our results show no statistically significant differences between o groups with regard to age duration of diabetes dose or administration of

Table IV
Age and duration of diabetes at the follow-up

Diagnostic group	Number	Age (in years) $\bar{x} \pm$ SEM	Duration of diabetes (in years) $\bar{x} \pm$ SEM
Total material	[illegible]	14.2 ± 0.2	[illegible]
Retinopathy	[illegible]	15.2 ± [illegible]	[illegible]
No retinopathy	[illegible]	14.3 ± 0.2	[illegible]

Department of Ophthalmology (Head Birgitta Zetterstrom) Hudding University Hospital Karolinska Institutet Stockholm Sweden

RESULTS OF PHOTOCOAGULATION IN DIABETIC RETINOPATHY AFTER LONG-TERM FOLLOW UP

BY

BIRGITTA ZETTERSTRÖM

Seventy three diabetics with retinopathy in whom one eye was treated by photocoagulation and the other was left untreated were followed up for 9 to 11 years Visual acuity visual field dark adaptation curves and intraocular pressure were recorded biomicroscopy and photography of the fundus were carried out Severe visual loss (< 0 1) was noted in 4% of the treated and in 9% of the untreated eyes Minor subjectively unnoticed scotomas were found at visual field examination in 18 of 40 treated eyes Dark adaptation curves showed abnormal values both in the treated and in the untreated eyes without any recordable difference No contra indicating long term complications of the photocoagulation treatment could be demonstrated

Key words diabetic retinopathy – photocoagulation – visual field – dark adaptation

hotocoagulation treatment of diabetic retinopathy has been found to have neficial effects according to the results of extensive well-controlled multicentre ials (Diabetic Retinopathy Study Research Group 1976 British Multicentre hotocoagulation Trial 1977 Hercules et al 1977) The risk of severe visual loss as reduced and no contra indicating complications of the treatment have so far een noted Meyer Schwickerath who was the first to introduce the photocoagula on method discussed at an early stage the cause of the favourable effect in diabetic

eceived November 1st 1979

retinopathy. As early as 1969 he suggested that the explanation might be ... result of scarring of some parts of the retina the metabolic conditions ... remaining untreated parts could have become more favourable. This ... has in part, been accepted and developed. The purpose of the present ... was to study the long term effect and any late complications of photocoagulation ...

Material and Methods

Over the period 1968–1970 156 patients were treated by photocoagulation ... of them were re-examined in 1979 that is 9 to 11 years after ... Eighty three of the original 156 patients could not be traced for various ... they had died (18) were too severely ill to be examined (9) moved (53) or did ... want to attend the follow up examination (3).

At photocoagulation in 1968–1970 only one eye was treated and the other ... was used as a control. At the start of the treatment period 58 of the 73 ... patients had proliferative retinopathy without growth of vessels into the vitreous ... cavity and without connective tissue. 15 had moderate to severe simple retinopathy, that is absence of neovascularisation but more or less profuse microaneurysms, haemorrhages and exudates. The retinopathy was of similar appearance in the treated and the untreated eye. The difference in visual acuity between the treated and the untreated eye was maximally 0.2. The eye with the lowest visual acuity ... selected for treatment. At the start of the treatment period visual acuity ... 0.5–1.0 in 70 and 0.4–0.1 in 3 of the 73 followed up patients.

The apparatus used was Zeiss Oberkochen photocoagulator. Apertures 3 and 4.5 were used and a total of 200 to 500 lesions were produced in each ... eye on two or three occasions.

At the follow-up examination the patients were asked about any ... the purpose of assessing any subjectively observed visual field defects or ... reduced dark adaptation. Visual acuity, media and fundus were checked ... recorded photographically in all the eyes. In one treated and eight untreated ... the fundus could not be photographically recorded due to opaque media ... visual field was examined in 40 of the patients. Dark adaptation curves ... Weeker's adaptometer were recorded for the treated and the untreated ... separately in 10 of the 73 patients. The ages of these 10 patients ranged from ... 60 years and visual acuity in both the treated and untreated eye was 0.4 ... intraocular pressure was measured in all the eyes by applanation tonometry.

Table I

Visual acuity of photocoagulation treated eyes and untreated fellow eyes before and after follow up for 9 to 11 years

Visual acuity	0 5–1 0	0 1–0 4	< 0 1
Treated Eyes			
1968–70	70 (96%)	3 (4%)	0 (0%)
1979	57 (78%)	13 (18%)	3 (4%)
Untreated fellow eyes			
1968–70	70 (96%)	3 (4%)	0 (0%)
1979	32 (44%)	23 (31%)	18 (25%)

Results

ial acuity of the treated and the untreated eyes at the start of treatment in 8–1970 and after follow up for 9 to 11 years is recorded in Table I It will be n that the treated eyes showed a percentage impairment of visual acuity but that re impairment (< 0 1) occurred in only three eyes after 9 to 11 years At the ck up in 1979 two of the latter three patients had also visual acuity < 0 1 in the reated eye and one had visual acuity of 0 3 in the untreated eye which means t only one patient had severe visual loss in the treated eye alone A larger portion of the untreated eyes showed impairment of visual acuity and 18 eyes l severe visual loss (< 0 1) (By χ^2 test according to MC Nemar $P = 0\ 0001$)

Distinct retinal atrophy with very narrow vessels and some optic atrophy were ed in 28 of the treated but in only five of the untreated eyes ($P \approx 0$) Careful microscopy at the follow up in 1979 revealed that neovascularisation was not sent in 17 of the 58 eyes with proliferative retinopathy treated in 1968–1970 In untreated fellow eyes neovascularisation of varying degree was noted at the lw up in all the eyes in which the fundus could be inspected In eight of the treated eyes the condition of the fundus could not be assessed because of vitreous emorrhage or cataract Of the 15 eyes with back ground retinopathy alone ated in 1968–1970 two had developed proliferative vascular changes at the llow up Of the 15 untreated fellow eyes 11 showed proliferative retinopathy at e follow up examination ($P = 0\ 002$)

The photocoagulation scars were highly atrophic mostly with intensive pigmen tion Photographic studies showed that the scars had also increased in size mpared with their appearance at one to three years after the photocoagulation

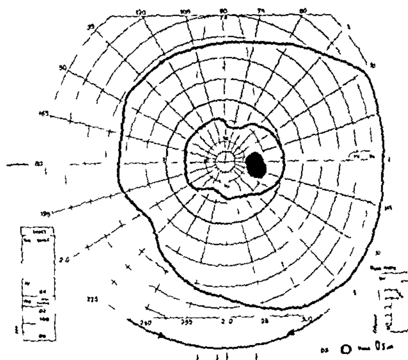


Fig 1

Visual field showing minor scotomas post photocoagulation treatment

Visual field tests using Goldman s perimeter with two isopters objective s[illegible] intensity of 4 and objective size I intensity 2 and screening of the blind sp[illegible] treated eyes revealed minor scotomas in 18 in which no symptoms had be[illegible] subjectively An example of a visual field from one of the patients ha[illegible] scotomas is demonstrated in Fig 1

Adaptation curves for 10 patients are shown in Fig 2 for the trea[illegible] for the untreated eyes It will be seen from these curves that there [illegible] recordable difference between the treated and the untreated eyes [illegible] showed pathological adaptation curves however and in no case did the [illegible] the normal threshold level of $10^2 \times 0\ 6$

In eight untreated eyes with visual acuity $< 0\ 1$ the intraocular p[illegible] 40–50 mmHg and in the rest untreated and all the treated eyes it was [illegible] mmHg

Rubeosis iridis was present in five treated and in 26 untreated eyes

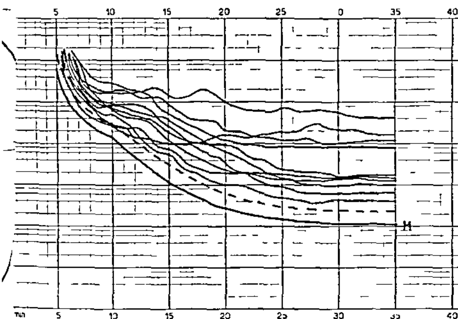


Fig 2

k adaptation curves recorded in the treated eye at 9 to 11 years after photocoagulation in diabetics between 40 and 60 years old M = threshold values in healthy individuals in this e range broken curve represents upper borderline of normal range of threshold values

Discussion

1e value of photocoagulation treatment in diabetic retinopathy has been re-atedly documented in extensive well-controlled studies Up to the present, owever the patients have been followed up for few years only Experiences from e large American study in 1976 showed that the results for the treated eye proved further with the time that elapsed after the photocoagulation

Klemen & Freyler (1979) report their results of a retrospective study comprising 9 diabetics who were followed up for 10 years after treatment by Xenon arc hotocoagulation of one eye The untreated fellow eye showed more severe fundus anges and impaired visual acuity The authors do not discuss any long term omplications of the treatment

The results obtained in the present study (Table I) show that a general npairment of visual acuity occurred both in the treated and in the untreated eyes

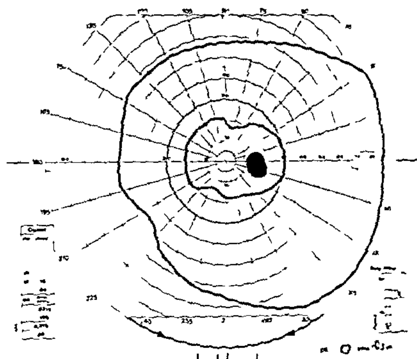


Fig 1

Visual-field showing minor scotomas post photocoagulation [illegible]

Visual *field tests using* Goldman's perimeter with two isopters [illegible] intensity of 4 and objective size I intensity 2 and screening of the [illegible] *treated eyes revealed* minor scotomas in 18 in which no symptoms had [illegible] subjectively An example of a visual field from one of the patients [illegible] scotomas is demonstrated in *Fig 1*

Adaptation curves for 10 patients are shown in Fig 2 for the treated [illegible] for the *untreated* eyes *It* will be seen from these curves that [illegible] recordable difference between the treated and the untreated eyes [illegible] showed *pathological* adaptation curves however and in no case did [illegible] the normal threshold level of $10^2 \times 0.6$

In eight untreated eyes with visual acuity < 0.1 the intraocular [illegible] *40–50 mmHg* and in the rest untreated and all the treated eyes [illegible] mmHg

Rubeosis iridis was present in five treated and in 26 untreated eyes

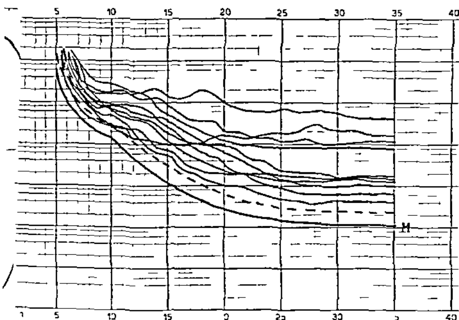


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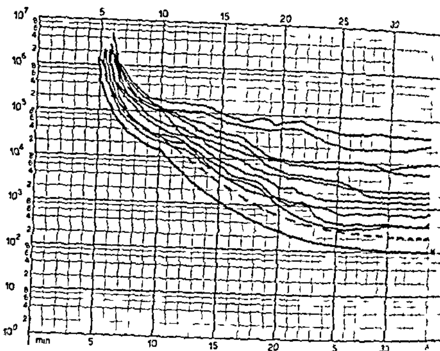


Fig 3
Dark adaptations curves recorded in the untreated fellow eye in the same group a [illegible]

but that severe visual loss was present in only three treated eyes (4%) after [illegible] years Severe visual loss occurred in 18 (25%) of the untreated eyes

The retinopathy was more marked in the untreated eyes Proliferative [illegible]pathy which at the start of the treatment period occurred in 58 of the 73 [illegible] eyes was present in 43 eyes at the follow up examination which means a [illegible] risk of haemorrhage for 15 eyes In 1979 proliferative retinopathy occurred [illegible] of the untreated eyes i e an increased risk of haemorrhage for 11 eyes

Distinct retinal atrophy with very narrow vessels and some atrophy of the [illegible] were noted in well over one third or 28 of the treated eyes and in [illegible] untreated This fact supports the hypothesis that after photocoagulation [illegible] large parts of hypoxaemic retinal tissue are destroyed the risk of [illegible] proliferative neovascularisation would diminish and that hence the [illegible] the remaining retinal tissue might improve One possible cause of the [illegible] of photocoagulation could be that in some cases it leads to retinal atrophy of the same type as that occasionally seen after diabetic retinopathy of [illegible] standing in which it seems to undergo spontaneous self healing where the [illegible] metabolic activity is reduced and oxygen demand is lessened In these [illegible]

ssible that because of reduced numbers of viable cells in the retina there is an ·ficient amount of vasoproliferative factor produced to stimulate neovasculari n

ireful analysis of the visual field in 40 of the treated eyes showed minor ctively unnoticed scotomas in 18 The Diabetic Retinopathy Research Group ›rt (1976) that one year after the treatment 44% of the Xenon arc treated eyes ·visual field scores in the range of 240–500 degrees Frank (1975) reports al field defects after extensive argon laser coagulation of 24 eyes in which or defects not subjectively noted were present in 21 and severe visual field loss ectively noted in three eyes In the present material the occurrence of severe al defect as a complication seemed to be insignificant The varying degree of al defect between different materials is probably due to more or less aggressive tment with respect to extent and effect

he ten patients whose dark adaptation was studied were selected by visual ity and age for comparison with eyes of healthy controls in the same age range ·re was no recordable difference in the appearance of the curves between the ted and the untreated eyes All the eyes showed pathological curves which were er than normal particularly towards the end of the time required for normal k adaptation This is in agreement with the observations by Zetterstrom & tterberg (1973) who examined 20 diabetics with retinopathy before and several ıths after photocoagulation and found no significant improvement or impair ıt of dark adaptation Nor did the adaptation pattern in these eyes seem to have nged after a long observation period (9 to 11 years) on comparison with the reated eyes None of the 20 examined patients reported any increased difficulty eeing at night or in getting used to the dark This observation was confirmed by ısen & North (1979) who studied the dark adaptation of 35 diabetics

n conclusion the results in the present followed up material show that even after ›ng observation period the treated eyes had retained better visual acuity that re were fewer eyes with severe visual loss and that the risk of catastrophic morrhage was reduced in comparison with the conditions of the untreated eyes r did the treatment seem to have been followed by any contra indicating g term complications

References

ıish Multicentre Group (1977) Proliferative diabetic retinopathy Treatment with Xenon rc photocoagulation *Brit Med J* 1 739–741

betic Retinopathy Study Research Group (1976) *Amer J Ophthal 81* 383–396

nk R N (1975) Visual fields and electroretinography following extensive photocoagula ion *Arch Ophthal (Chicago) 93* 591–598

Henson D B & North R V (1979) Dark adaptation in diabetes me [illegible] Br J [illegible] 539–541

Hercules B L Gayed I I Lucas S B & Jeacock J (1977) Peripheral retinal [illegible] treatment of proliferative diabetic retinopathy *Brit J Ophthal 61* 5[illegible] 5[illegible]

Kleman U M & Freyler H (1979) Diabetische Retinopathie 10 Jahre nach [illegible] *Klin Mbl Augenheilk 174* 489–492

Meyer Schwickerath G R E & Schott K (1969) Diabetic retinopathy and ph[illegible] *Mod Probl Ophthal 8* 492–499

Zetterstrom B & Gjotterberg M (1973) Photocoagulation in diabetic retinopat[illegible] reference to its effect on dark adaptation *Acta ophthal (Kbh) 51* 51[illegible] 519

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A PRESSURE LOWERING EFFECT OF RETINAL XENON PHOTOCOAGULATION IN NORMOTENSIVE DIABETIC EYES

BY

SØREN NICOLAI SCHIODTE ERIK SCHERFIG and OLE I NISSEN

In 10 diabetic patients with normal intraocular pressures the effect of monocular panretinal xenon photocoagulation was recorded with the applanating suction cup tonograph applied bilaterally One month after the treatment the photocoagulated eyes showed an average decrease in pressure of approximately 3 mmHg which was statistically significant ($P < 0.001$) when compared to the untreated fellow eye On a percentage basis the falls were of a similar magnitude (approximately 25%) as those observed by others after photocoagulation in neovascular glaucoma

Key words applanating suction cup tonograph – diabetes – intraocular pressure – photocoagulation

s shown by Laatikainen (1977) that a panretinal xenon photocoagulation has a ficial effect on the intraocular pressure of eyes with neovascular glaucoma In resent study we have demonstrated that this effect is not only due to the special of the blood circulation of the eye in this severe disease – actually a xenon ocoagulation treatment also reduces the pressures of normotensive diabetic

ved November 15th 1979

Material and Methods

In this study one eye was treated while the other eye served as a co... d. The... pre-treatment examination 10 patients were selected (eight males and t... fe... age 35 years) who had fairly symmetrical conditions regarding intra... pre... and slight degrees of proliferative diabetic fundus changes. The ... tonograph applied bilaterally was used for the pressure measurement ... accurate comparison between fellow eyes, both with respect to pre... amplitudes. All the pressures given are the steady state (equilibrium) pre... obtained by continuous recording with this method (for details see ... presented pressures are the averages of such registrations made before and ... interchange (left/right) of the cups. The distribution of the intraocular pre... patients appears from Table I, columns 3–4.

The photocoagulation of the trial eyes was arranged in two steps with a... month. The same eye was photocoagulated both times. The IOP of both eyes ... approximately 24 h before and after each photocoagulation. Final ... IOP ... was made one month after the second treatment. The non-photoco... eye functioned as control eye. A Zeiss xenon photocoagulator, model ... clinically satisfactory burns were normally obtained by adjusting the ... diaphragm 4.5, iris diaphragm I and power output grundlast III. The ... panretinal and special care was taken not to let the burns overlap. The intensity ... light was kept so low that the appearance of double halves was avoided. On the ... the intensity was high enough to produce an immediate whitish bleach... followed later by an easily detectable pigmented scar.

All the treatments were performed by one of us and to avoid an asymmetr... from the mydriatics (phenylephrine 10% and Mydriacyl® 0.5%) both pupils ... eyes to be treated were anaesthetized with 3 ml 2% lidocain conta... ephrine and 1000 I.U. Penetrase® injected retrobulbarly.

Results

The pressure (IOP) of the experimental eye and the control eye of the ... before and after the treatments are given in Table I. On an average the ... experimental eye was 0.8 mmHg above that of the control eye be... treatments. However, one month after the first treatment the ... reversed, the IOP of the experimental eye was now below that of the c... and this remained so. The IOP of the control eye seemed unaffected.

A statistical treatment (Student's *t* test) of the differences between the ... experimental eyes and the control eyes shows that there was a significant ... in IOP of the experimental eyes one month after the first treatment and ... month after the second treatment, when compared to the pre-treatment ... From a statistical point of view there was no additional pressure ef... coagulations of the second treatment ($P < 0.05$).

[illegible]

Case No	Age (years)	Pre-treatment IOP (mmHg)		IOP 24 h after 1st photocoagulation (mmHg)		IOP 1 month after 1st photocoagulation (mmHg)		IOP 24 h after 2nd photocoagulation (mmHg)		IOP 1 month after 2nd photocoagulation (mmHg)	
		Eye to be treated	Control eye	Treated eye	Control eye	Treated eye	Control eye	Treated eye	Control eye	Treated eye	Control eye
1	37	13.5	13.5	10.0	12.0	8.0	10.0	10.0	12.5	8.0	10.0
2	21	11.0	*11.0	15.0	11.0	11.5	12.0	12.0	10.5	12.0	11.0
3	27	9.0	*10.0	11	12.0	9.5	11.5	17.5	12.0	9.5	10.0
4	32	*19.0	18.0	15.0	10.5	14.0	16.0	13.5	15.5	12.0	16.0
	19	17.5	13	28.0	15.0	13.0	13.5	16.5	16.5	11.0	12.0
6	32	13.5	13.5	6.0	8.0	7.0	10.0	9.0	11.0	7.5	11.0
7	42	11.0	*13.0	10.5	10.0	10.5	11.5	11.0	13.5	11.0	13.0
8	36	*9.5	10.5	11.5	8.0	8.5	9.5	7.0	8.0	10.5	12.5
9	10	*12.0	12.0	10.5	10.5	12.5	12.5	12.0	15.0	10.5	15.5
10	30	11.5	11.0	12.5	11.0	10	11.0	11.0	13.5	8.5	11.5
Mean	35	13.1	12.6	13.1	11.1	10.4	11.8	12.0	12.8	10.1	12.6
Mean difference (exp control)		0.75		1.15		−1.10		−0.85		−2.50	
s.e. of difference		0.51		1.13		0.30		0.45		0.15	
Different from pre-treatment period for				$P > 0.05$		$P < 0.005$		$P > 0.05$		$P < 0.0005$	

* Right eye

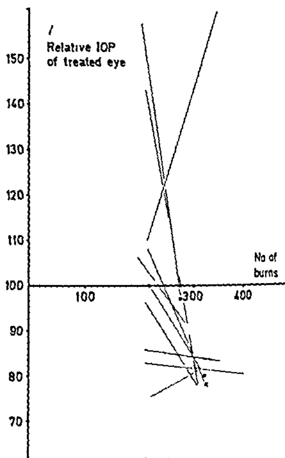


Fig 1

The *acute* effect of monocular xenon photocoagulation on relative intraocular pressure of the treated eye Abscissa number of coagulations Ordinate relative pressure of treated eye expressed by the percentage given in Results (eq 1) ● IOP measured 24 h after the first treatment × IOP measured 24 h after the second treatment in the same eye between treatments one month

In order to illustrate this effect of photocoagulations on IOP it is expressed pressure ratio $IOP_{exp}/IOP_{control}$ after the treatments in per cent of the ratio obtained before the first treatment (Figs 1 and 2)

$$\frac{[IOP_{exp}/IOP_{control}] \text{ after treatment}}{[IOP_{exp}/IOP_{control}] \text{ before first treatment}} \times 100\%$$

– a percentage of 100 means no effect a percentage below 100 means a pressure lowering effect of the treatment

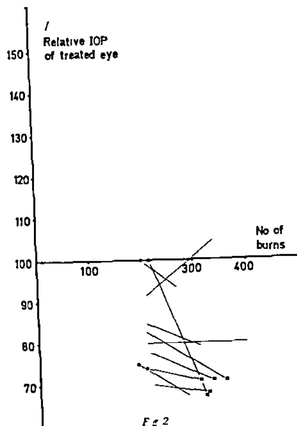


Fig 2

h on e effect of monocular xenon photocoagulation on the relative intraocular pressure l of the treated eye Abscissa number of coagulations Ordinate relative pressure of the d eye expressed by the percentage given in Results (eq 1) ● IOP measured one month the first treatment × IOP measured one month after the second treatment in the same eye Time between treatments one month

rom Fig 1 it may be seen that the *acute* effect of the treatment varied iderably Twenty four h after placing on an average 205 coagulations per eye patients showed a relative pressure rise of 7 to 59% in the treated eyes (value of tion above 107 to 159%) four patients a fall of 3 to 25% in one patient the tive pressure was unchanged Twenty four h after the second treatment (on an rage another 122 burns) one patient showed a pressure rise of 62% another was ost unchanged and in the rest (8 eyes) the relative pressures of the treated eyes ained low though on a slightly higher level than immediately before the second otocoagulation

The *chronic* changes in pressures were more consistent (Fig 9) One mont the first treatment eight of the 10 eyes showed falls in pressures of 8 to % eyes did not change When examined one month after the second t majority (9) of the experimental eyes again showed relative falls situation before the first treatment The decreases were 7 to 39% in pressure increased by 6%

Discussion

One month after treatment with the xenon lamp the photocoagulator probably healed and changed to scars At this time nearly all of the treated e reacted with a pressure fall (Fig 2) From a pre treatment level of 13 4 two photocoagulation treatments caused an average pressure decline of 3 3 (the control eyes did not on an average show any change in pressure o columns 3–4 with 11–12 in Table I)

To explain a pressure decrease of 3 3 mmHg a very considerable decrea take place in the aqueous formation or in the resistance of the aqueous channels because a depression of these parameters even to zero would p make the IOP of the recumbent patient to fall only to a value near the ep sc pressure viz about 10 mmHg Accordingly a panretinal photocoagulat cause a profound disturbance in the inflow outflow mechanisms of the humour

On a percentage basis the pressure decreases in our experiments are of magnitude as those seen after photocoagulations in neovascular glaucom kainen 1977)

A number of possibilities which are under investigation may expla n th The immediate necrosis or the later scarification due to the burns m ght larger choroidal arteries or nerves supplying the ciliary body res depression of the aqueous formation Other findings not publ shed indicate extensive damage to choroidal and ciliary structures a reductio ocular pulse amplitude a fall of the corneal sensibility a dilated pupil ma light and a reduced range of accomodation

Rogell (1979) observed a high frequency of internal ophthalmopleg photocoagulation with the argon laser Furthermore histological examina choroidal casts from fresh xenon photocoagulated rabbit eyes revealed larger choroidal vessels in addition to a destruction of the choriocapillar 1979)

An increased hydraulic conductance of existing or new formed pathwa

ous humour from the eye was a second explanation for the pressure fall after n photocoagulation Such increase might be due to an absorption of aqueous across the choroidal retinal cicatrices or to a traction on the trabecular work from a scarified choroid A third explanation is a fall in the pressure of leral and aqueous veins caused by a lowered blood perfusion of the eye ht tonographic studies may throw light on these problems

s possible that also the retrobulbar aeaesthesia might play a role in the pressure One possibility is that the retrobulbar anaesthesia by itself is responsible This ver is an unlikely explanation since it has been shown that the pressure ne seen in both glaucomatous and normal eyes after administration of obulbar anaesthesia is only of very short duration not more than one hour and lf (Snydacker et al 1954 de Roetth & Carroll 1955 Mees 1940) Another ibility is that the retrobulbar anaesthesia intensifies the effect of xenon ocoagulation Hørven (1978) and Pohjanpelto (1979) described a pronounced ease in the ocular pulse amplitudes immediately after a retrobulbar injection of al anaesthetic Supposing that this indicated a lowered choroidal blood flow cted by the intraorbital presence of anaesthetic fluid an eye treated in a obulbar anaesthesia may be more extensively affected by a photocoagulation tment because an insufficiently perfused tissue will be less resistant to heat stigations on the effects of treatments using the argon laser with and without obulbar anaesthesia might give an answer

he immediate effect of the coagulations is known to be hyperaemia and dation of the choroid (Diddie & Ernest 1977 Kolker & Hetherington 1976) s may explain why we find relative increases of IOP 24 h after the treatment in a nber of patients (Fig 1) These acute effects of photocoagulations will not be ther discussed in this article

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References

de K R & Ernest T J (1977) The effect of photocoagulation on the cho o dal sculature and retinal oxygen tension *Amer J Ophthal 84* 62–66

ven I (1978) Ophthalmic artery pressure during retrobulbar anaesthesia *Acta ophthal* *Kbh) 56* 574–58

ker A E & Hetherington J (1976) Becker Shaffer s Therapy of the Glaucomas 4th dition p 200 C V Mosby Company Saint Louis

Laatikainen L (1977) Preliminary report on effect of retinal panphotocoag- rubeosis iridis and neovascular glaucoma *Brit J Ophthal 61* 278–284

Mees G (1940) Uber den Einfluss der retrobulbaren Anasthesie auf den Augeninne- *Klin Mbl Augenheilk 104* 223–230

Nissen O I (1980) Bilateral recording of human intraocular pressure with an applanation suction cup tonograph *Acta ophthal (Kbh) 58* 317–397

Pohjanpelto P (1979) Pulse induced intraocular pressure variation and retrobulbar an- aesthesia with and without adrenaline *Acta ophthal (Kbh) 57* 136–144

de Roetth A & Carroll F D (1955) Effect of retrobulbar procaine injection on a- humor dynamics *Arch Ophthal (Chicago) 53* 399–403

Rogell C D (1979) Internal ophthalmoplegia after argon laser panretinal photocoag- *Arch Ophthal (Chicago) 97* 904–905

Sato T (1978) Scanning electron microscopic observation of choroidal angioarchitec- pigmented rabbit after xenon photocoagulation I Observation immediately after coagulation *Fol Ophthal Japan 29* 55–39

Snydacker D Deutsch W E & Bayard W L (1954) Various anesthetic agents- retrobulbar injections *Arch Ophthal (Chicago) 51* 473–480

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ATERAL RECORDING OF HUMAN INTRAOCULAR PRESSURE WITH AN IMPROVED APPLANATING SUCTION CUP TONOGRAPH

BY

OLE I NISSEN

An improved applanating suction cup for continuous recording of human intraocular pressure is described The new cup adheres better is easier to calibrate and is simpler to handle mainly due to a d fferent curvature of the applanating surface The interspace between the applanating and the applanated surface in which the pressure is measured is continuously flushed with saline from a flow system (Intraflo®) connected to the dome of the pressure transducer The suction that attaches the cup to the cornea is – as in the previous model – provided by a saline filled tube hanging from the cup In 51 human cadaver eyes the calibration for static pressures and pressures oscillating up to 1?4 cycles per m n was intraocular pressure 0 9 × cup pressure –3 (mmHg) r = 0 99э The cup reduced ocular rigidity by 5% only and increased the intraocular pressure transiently by 4 mmHg when applied Simultaneous bilateral recordings were obtained in 400 normo- or hyper tensive eyes from ?06 subjects The cup was atraumatic and the method can be strongly recommended when accurate bilateral pressure recordings are desired for periods up to one h in sup ne subjects At intraocular pressures above 3э mmHg the tonograph may underestimate the pressure under certain unfavourable conditions

Key words continuous pressure measurements – intraocular pressure – instrument – pulse amplitudes – tonograph

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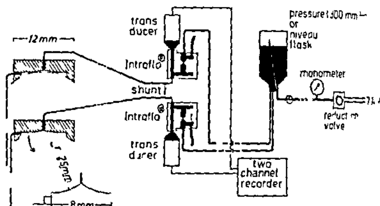


Fig 1

The setup for bilateral pressure measurement in human subjects The two suction cups shown to the left the position of the cornea is indicated underneath the upper cup The applanating surface is shown in detail below the curvature is exaggerated for clearness the radius of the correct curvature The resistance capillary of the Intraflo® unit is by pulling at its rubber rod the by passes are indicated by dashed lines Seven atmosphere air pressure was available in the pressure system of the hospital The shunt is used calibrations

The applanating suction cup tonograph (Nissen 1977a) is suitable for bilateral recording of the intraocular pressure in supine subjects for periods of up to The two lucite cups adhere to the corneas by the negative pressures produced water columns in tubes hanging from the cups The improved model has now been tested in 80 eyes of human cadavers and in 206 subjects with normal or elevated intraocular pressures and appears to be an accurate and well tolerated instrument We will begin by summing up the improvements

1) While the depth of the earlier cup had to be adjusted to the corneas by turning its central applanation part in a screw thread the new simpler cup is made in piece A standard cup fits the eyes of five sixths of the patients a flat or a cup has to be used for the remainder

2) Compared to the previous model the new cup bends the cornea less at the periphery of the applanated surface due to the steeper curvature of the applanating surface (Fig 1) This means that the repulsive force caused by the rigidity of cornea substance becomes less i e at the same intraocular and suction pressures cup adheres better

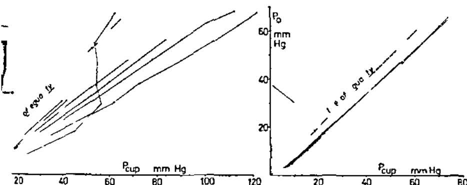


Fig 2

effect of change in curvature of the applanating surface Left A plane applanating ice was mounted in the screw cup described by Nissen (1977a) and screwed in stepwise to ge the applanated surface (bottom curves correspond to small applanated surfaces) t The new curved applanating surface is mounted in the screw cup and the procedure peated Each set of lines is made in one human cadaver eye For details see Nissen (1977a) and the introduct on

The curvature of the applanating surface is also designed to make the calibra i line independent of the diameter of the applanated area this means that the he calibration is used with the three cups mentioned above The effect of making surface cone shaped and convex (Fig 1) may be explained thus We know that if applanating surface is plane and the applanated area small a relatively large rt of the pressure in the interspace is used to bend the cornea a smaller part to utralize the intraocular pressure vice versa if the applanated area is large (Fig 2 t) Therefore if the applanating surface is designed to bend the cornea less at all applanated areas than at large areas this effect is counteracted and the libration lines for different applanated areas may be brought to fall on top of each her (Fig 2 right)

The present model of the cup has only one central connection This makes the indling of the cup easier The infusion pump is replaced by a compact continuous ish system (Intraflo®) which fits the transducer dome and is available in erilized sets

Methods

The general principle of the t nograph has been described n the accoun b N e to wh ch the reader is referred

The d mens ons of the new cup are sl own n F g 1 In the deep and the flat applanat ng surface was d splaced respect ely up and down b 0 175 mm. The the left cup were each connected to a pressure transducer (S a ham P23 Db of S last c® tube (d 0 61 mm o d 1 19 mm) a T f t ng and a ontinu u fl (Intraflo® Sorenson Research Co) f tt ng the Luer connection of he transducer When the two flush systems were fed w th a sterile R nge s solu on (pe l e 1 sod um 156 meks chloride 4 meks potass um and 4 6 mek ca cium) a pressure of mmHg approx matel 50 µl m n were del ered to each cup for ma n enan e of the d scs between applanating and applana ed surfaces W th th s flow of flu d the pressure from the transducer to the cup was 0 to 0 4 mmHg The two T f ings were connected short p ece of S last c® tube (tl e shunt n F g 1) suppl ed w h a clamp When th removed during the meas remen s both transducers were exposed to the same pres the two recorder pens could be adjusted exactl to the same level n order to augment accuracy of a subsequent comparison between the two eyes

During the electric adjustment of the transducer recorder s s ems before th measure ments the common pressure flask was use l as a le el reservo r Then the a n the bottle opened to the a mosphere through the stop-cock the tubes to the cups were p nched off shunt between the T f ttings was opened an l the res tance cap llary of one of the con flush un ts was by passed

Pieces of S last c® tubes 95 cm long and of tl e same d mens ons as those mentioned emerged from the s des of the cups and hung down by 90 cm They crea ed a se pressure of approx mately 15 n mHg the la eral spaces wh h kept he cups on the cor (F g 1 N ssen 1977a)

The transducers were connected to a two channel Kompensograph® servorecorder frequency response of the tube transducer servorecorder sys em allowed a egistra pulse ampl tude of the l v ng eye By means of a pressure genera or prod cin sin pulse d fferent frequencies and of a real s c magn tude we regis ered a reduction of only ampl tudes at 10 cycles second

When static pressure cal brat on curves were de erm ned on human cada e eyes was stud ed at a time V a th n needles the anter o hamber of he eye was connected level flask and to tl e same transducer as tl e cup (le ribed b N ssen 197 a A zero pres level was def ned as that of the anter or chamber

The capab l ty of the eye-cup-recorder system to measure osc lla ng p essures was test human cada er eyes by record ng s multaneously the pressure n the cup P_{cup} and a an erior chamber P_C (two transducers were used) luring p es ure oscilla ions simul pulse pressures n o an l produced manually by an nterm ent ex ernal compres the eye

The volume compl ance of tl e eye sphere w th an l w hout a cup app ed wa tested b njections (and asp rat ons) of 5 µl of sal ne n o he anterior chamber of he cadaver through one cannula wl le record ng P_O by another (w h the connect on o the anter closed)

The pressure record ngs on olun eers and pat en s were made as prev usl des (Nissen 1977a) The local anaes het c (0 4% oxybuproca ne w hout preserva e 4 before and every 15 to 20 m n during measurements During ze o set ng of the

he shunt connecting the transducers was clamped and the usual 50 µl min of balanced lution flowed to each cup both lying in the internal canthus of the eyes Two types of tractors gave minimal compression of the globe the Barraquer model (e g Storz ments No E 4106-S) equipped with a loop of silk thread preventing the branches from ng too much and putting strain on the lids and the small Cook model (e g Klein ments No 59901) The increase in intraocular pressure produced by these speculae was ated during the recordings by lifting and gathering the branches a little to free them touching the globe and pulling the eye lids

Results

calibration line of the standard cup for static pressures is shown in Fig 3 The r equation was computed for P_O values below 50 mmHg by the method of least es The equations of the calibration lines for the deep and the flat cup were mined similarly and are given in the legend The three lines are hardly iguishable in a drawing Forty eyes from 22 human cadavers were used in this of the study

ie cup was able to measure oscillating pressures correctly In 32 series of lated pulse pressures on 11 human cadaver eyes (one single and five pairs) the between the artificially produced pressure amplitudes in the anterior chamber the corresponding pressure amplitudes in the central saline disc of the cup was ΔP_{cup} = 0 896 ± 0 043 (SD) n = 32 a ratio corresponding closely to the slope ie calibration line (Fig 3) The oscillations were produced at frequencies ing from 48 to 124 per min in the different series The ratio $\Delta P_O/\Delta P_{cup}$ was fected by these frequency variations

ie immediate effect on the intraocular pressure (P_O) of attaching the standard to the cornea with the usual suction pressure of 20 cm of water column was sured in 9 pairs of eyes and one single eye of human cadavers disconnected i the level reservoir Like other cornea touching tonometers the suction cup rmed the eye therefore P_O increased In the P_O intervals 5–10 11–20 and 30 mmHg an average increase of 3 9 mmHg (range 2–6 mmHg) was observed number of observations within each pressure range was n = 19 The average ease in the interval 31–40 mmHg was 3 5 mmHg (range 1 5–7 mmHg) 17 Fellow eyes responded with approximately the same increase the mean erence in the response being only 1 0 mmHg (range 0 1–2 0 mmHg) (The ght of the cup 0 4 g was too small to increase P_O This was tested by putting the on the cornea without applying suction no measurable intraocular pressure ement ensued)

low the cup affected the volume compliance of the eye sphere was estimated

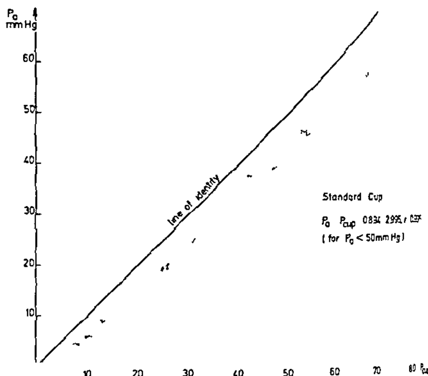
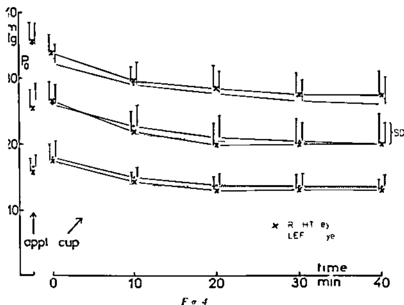


Fig 3

The calibration line for the standard cup calculated by the method of least square[?] 460 measurements on 38 human cadaver eyes Abscissa The pressure in the [illegible] between applanating and applanated surface (P_{cup}) ordinate The pressure in the [illegible] chamber of the eye (P_O) Similar calibration lines were determined for the flat and [illegible] cup Their equations were respectively $P_O = 0.869 \times P_{cup} - 2.3$ (mmHg) coefficient correlation $r = 0.996$ $n = 319$ and $P_O = 0.901 \times P_{cup} - 3.03$ (mmHg) $r = 0.9$[illegible]

from 410 single intracameral 5 µl injections (and aspirations) in the pressure ra[illegible] 10–20 21–30 and 31–40 mmHg on five pairs of human cadaver eyes Without cup on the cornea P_O rose on an average by 4 1 5 3 and 6 3 mmHg respectively With a cup attached to the cornea the pressure rose 8 6% 4 8% and 5 3% [illegible] indicating a minor increase in the volume compliance In terms of percentage change in ocular rigidity (as defined by e g Duke Elder 1968) the effect of the deformation were falls of 6% 4% and 4% respectively The changes were statistically significant ($P < 0.01$)

The effect on the calibration equation of changing the suction pressure or the flow of saline to the cup was just as small as with the previous model and as before



F g 4

le course of intraocular pressure registrations in 93 supine subjects The first readings de by Perkins tonometer (left appl) and the curves by the suction cup tonograph right cup) The dotted curves are hypothetical pressure declines see discussion

ias no effect of increasing the temperature from room temperature to 37°C 1 1977a)

ptable bilateral pressure recordings were obtained from the eyes of 200 out living human subjects (37 with glaucoma, 49 with intraocular hypertension e volunteers the others were normotensive patients 78 were of the female fany of the examinations did not require a recording of a long duration er in 93 subjects the recordings lasted 40 min or more They were divided in lowing groups according to the Perkins applanation pressure measured 2 to n prior to the recordings 10–20 (n = 23) 21–30 (n= 43) and 31–40 5 (n = 27) *Within each group the corresponding suction cup recordings* iveraged at times 0 10 20 30 and 40 min The result is shown in Fig 4 er with the average readings obtained by the Perkins applanation tonometer rdinate is the Perkins tonometer Po pressure or the Po recorded by the 1 cup tonograph using the following common calibration for all three cup i (compare Fig 3) $P_O = 0\ 9 \times P_{cup} - 3$ (in mmHg) In Fig 5 are shown 348 comparisons between the Perkins applanation readings and the start Po

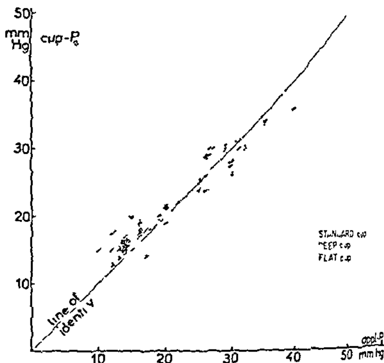


Fig 5

The correlation between the Perkins tonometer readings (abscissa) and the
measured with the cup (ordinate) using the usual calibration $P_O - 0.9 \times P_{cup}$ 1
The former measurements preceded the latter by 9–10 min

pressures measured by the suction cup (using the calibration above) Four
recordings had to be made with the deep cup six with the flat cup the
were done with the standard cup

The pressure amplitudes due to the beats of the heart measured with the
cup averaged 2 04 mmHg (range 1 5–3 2 mmHg) in 17 normotensive
students

During recording the cup could slide to an excentrical position on the cornea
the two cups could change places without affecting pressure levels or
amplitudes Attempts to extend the period of measurement beyond 50
were unsuccessful due to inconvenience referred to the lid retractors and the
freedom of eye movements The cup never produced more severe
abrasions than those seen after a few Goldmann applanation readings, and
discomfort afterwards when the effect of the local anaesthetic had disappeared
was normally limited to a couple of hours sensation of a conjunctival foreign body

contact of the lid speculae with the globe resulted in a mean increase in Po of ıHg (range 0–2 mmHg n = 17) due to compression – less in old persons onic lids and at high intraocular pressures

Discussion

xperiments on eyes from human cadavers show that the new tonograph properly calibrated (Fig 3) records static intraocular pressures as well ıng pressures at least up to a frequency of 124 cycles min Since there ı reason to believe that the calibration is valid in living eyes we are convin e are dealing with an instrument that is able to record correctly both pres and pulse amplitudes in the eyes of the patients. The use of the press zing shunt during an actual measurement permits an adjustment of the ler pens to exactly identical positions at identical pressures This ma ment extraordinarily sensitive to small pressure differences betw e g in studies with an experimental eye and a control eye (Schmerl

e applanating suction cup deforms the eye somewhat more than a G nation tonometer Thus the standard cup produced in inc d stop-cock) pressure of cadaver eyes of 3 9 mmHg it intra 31 mmHg and increments of approximately 3 5 mmHg at press d 40 mmHg while Goldmann s or Perkin s tonometer ure by only 0 4 mmHg in the lower and 0 8 mmHg in th (calculated from a volume displacement of 0 5 µl Duke r rigidity of E = 0 0215)
cordingly we would expect that in live normotensive ure measured by the standard cup were on average 3 er than the Perkins applanation pressure just trid sures the difference should be approximately 3 5–0 cup augmented the intraocular pressure by about tw dard cup Therefore with the deep cup the figures s Hg In the high pressure range and for the deep cup t lled on all occasions (Fig 5) a few of the poin iderably below the line of identity This may have m he higher pressures more than one trial was freque and sometimes the standard cup had to be rep ses in Fig 5) because the comparatively large app

the former resulted in a repulsion by the tense cornea This added tr manipulations and delayed the start of a successful recording probabl more prominent the so-called pressure lowering effect of repeated appla (Moses 1975) In a few cases the applanated surface might have been ins For instance this might happen when an astigmatism in an eye with an inr hypertension necessitated a shift to the deep cup with the result that the ap area became small and irregular In normotensive eyes a rather pro astigmatism was compatible with measurement with the standard cup

As the (closed stop-clock) pressure in the eyes of cadavers rose 3 to 1! when the cup was put on theoretically we should expect that in live eyes a of such magnitude was gradually lost as the pressure decays towards th brium level But the fall was actually 5–6 mmHg (Fig 4) The pressure on from the lid speculae can explain approximately one third (0 6 mmH discrepancy between the predicted and the actual pressure decrease The be owing to a transient increase in the tonus of the eye lids when t place and/or to the fact that the subjects relaxed when they di examination was painless Not rarely the examinee tended to fall asl showed itself immediately as a decrease in the pressures of both eyes

In live normotensive eyes the pressure reached its equilibrium level in 15 min in hypertensive eyes in less than 20 min or 30 min (Fig 4) Suc pressure falls harmonize with our ideas of the magnitude of the flow o humour and the volume compliance of the coats of the eye (making allo other minor factors also taking part in the pressure fall as mentioned a illustrate this in Fig 4 dashed curves are drawn which are calcula ed from integrated Friedenwald equation (Davanger & Holter 1967 Nissen 19 basis of outflow conductances of 0 06 0 12 and 0 25 µl min⁻¹ mmHg tively (from the top) and an ocular rigidity of E = 0 0?15 In the calc pre suppose that the sudden volume displacement produced by the atta the cup is equivalent to a step input e g an injection of a volume of flu eye and also that the ocular rigidity is unaffected by the presence of which is almost true see Results

Acknowledgments

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References

er M & Holter O (1967) Intraocular pressure in non-equilibrium states Acta ophthal) 45 510–524

Ider S (1968) The physiology of the eye and of vision In System of Ophthalmology IV pp 233 264 Henry Kimpton London

R A (1975) Adler s Physiology of the Eye p 192 6th edition Mosby St Louis

O I (19 7a) Continuous recording of the intraocular pressure in human and rabbit with a simple applanating suction cup Acta ophthal (Kbh) 55 750–760

O I (1977b) Model computation of the effect of arbitrary variations in aqueous ow outflow conductance ocular rigidity and episcleral vein pressure on ocular sure Acta ophthal (Kbh) 55 761–770

te N Scherfig E. & Nissen O I (1980) A pressure lowering effect of xenon ocoagulation in normotensive diabetic eyes Acta ophthal. (Kbh) 58 369–376

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ELECTRORETINOGRAPHY BY SKIN ELECTRODES AND SIGNAL AVERAGING METHOD

BY

EILA MUSTONEN and ILMAR SULG

In the investigation of suspected visual disorders ERG is of considerable value A simplified method for clinical electroretinography by non-corneal electrodes is presented The latency and amplitude values were measured in 99 normal subjects Using skin electrodes and signal averaging we can record without discomfort to the patient an electroretinogram with a waveform and time relations similar to those obtained by corneal electrodes Non-corneal ERG is useful for infants children as well as sensitive adult patients and is also applicable after recent eye surgery and in cases of infection or injury of the anterior segment Since non-corneal electrodes do not obstruct the stimulus light or cause refractive change they are advantageous when ERG is recorded simultaneously with visually evoked cortical response (VER) When it is important to stimulate only one eye at a time in flash VER the adequacy of the cover is verified by the absence of an ERG from the covered eye

Key words digital computer – ERG – signal averaging – skin electrodes VER

Motokawa & Mita (1942) reported that the ERG could be recorded from 2 non-corneal electrodes one attached to the bridge of the nose and the other temple near the eye being investigated but such small signals are usually masked by larger amplitude background activity The first averaging of ERG carried out in 1961 by Armington et al with an analog averager using cond... Tepas & Armington (1962) reported that averaged potentials picked

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des near the canthi of the eye have a waveform similar to the ERG recorded ineously with a contact lens

bson et al (1962) gave the first report of the use of digital computer que for recording clinical corneal electroretinogram Nagata & Jacobson found that the amplitude of the averaged ERG recorded from the skin de was greatest when the active electrode was placed on the lower lid and the nce electrode on the earlobe The waveform and the time relations were the as those recorded with a contact lens electrode Jacobson et al (1966) red non-corneal skin electrodes with a contact lens electrode and a hook d eyelid retractor hung over the lower lid They used a pair of silver disc odes attached about 5 mm from the external and internal canthi of the eye he temporal electrode used as the active one The amplitude of the response ed with the hook electrode was approximately three times as high as that of in electrode and about 65% of the magnitude obtained from the contact lens ode The blink artifact was more manifest in the record from the hook ode than from the skin electrode or from the contact lens

ent advance of averaging computers has made it possible to clinically evaluate isually evoked responses (VER) obtained from occipital electrodes with flash pattern reversal stimulation We needed a comfortable and easy method for rding simultaneously retinal responses (ERG) Non-corneal electrodes are also cable *in children* without general anaesthesia or sedation and averaging nique with digital computer has made it practicable to record ERGs from skin rodes Because one indication for simultaneous ERG and VER studies was the operative examination of the patients referred for vitrectomy we especially led normal values of retinal responses to bright light flashes The normal range ERG parameters recorded with our non-corneal technique is reported in the ent paper

Material and Methods

wenty two normal subjects (43 eyes) 19 women and 3 men between 21 and 58 s of age were examined for measuring normal amplitude and latency values of ERG by corneal skin electrodes and signal a eraging technique Their pre-examination included al acuity tests and refraction Friedmann and Goldmann visual fields Farnsworth otomous test Panel D 15 and Farnsworth Munsell 100-hue test as well as slit lamp and dus examination

fter pre adaptation in weak room illumination (2 5-3 lux) for 25 min followed by 5 min in kness the subject was stimulated with 10 flashes (1500 lux) of 10 mseconds duration and nsity of 0 2 joule from an Elema Siemens photostimulator (EMT 72?) with a l ghted area 160 x 325 mm giving white light flashes with 15-second intervals 20 cm in front of the

Table I

The latencies (measured from the stimulus-on) and the ampl tudes of a- and b-wave b-wave amplitude measured from the peak of the a wave) n non-corneal ERG from lower lid skin electrodes in 22 normal subjects (43 eyes) with st mula ion b 1 15 second intervals and same parameters in 15 of normal subjects (29 e es) with by 32 flashes at 2 Hz frequency Flash intens ty 0 2 joule

	Latency (msecond)				Ampl tude uV			
	a wave		b-wave		a wave		b-wave	
	Mean SD	n	Mean SD	n	Mean SD	n	Mean SD	
10 flashes at 15 second intervals (0 2 joule)								
Right eye	10 0 ± 2 19	(22)	39 8 ± 2 76	(22)	11 6 ± 6.50	(22)	31.5	13.2
Left eye	9 5 ± 1 42	(21)	39 6 ± 3 21	(21)	12 3 ± 5 42	(21)	33	+ 13.4
Average R & L eye	9 8 ± 1 81	(43)	39 7 ± 2 99	(43)	11 9 ± 5 96	(43)	39 6	13.3
32 flashes at 2 H frequency (0 2 joule)								
Right eye	9 3 ± 1 49	(15)	39 6 ± 2 71	(15)	6 4 ± 3 35	(15)	94 0 + 11.9	
Left eye	10 2 ± 2 15	(14)	39 8 ± 2 19	(14)	8 0 ± 3 9	(14)	95 8 + 11.6	
Average R & L eye	9 7 ± 1 82	(29)	39 7 ± 2 45	(29)	7 2 ± 3 5	(29)	94 9 + 11.9	

subject s eyes Pupils were not dilated Each eye was st mulated separately the o carefully covered by an eye patch the adequacy of the cover was verif ed by the abse ERG from the covered eye Another averaged ERG was then recorded in 15 of subjects (29 eyes) with stimulation by 32 flashes (intensity of 0 2 joule) at 2 Hz frequ simulataneous VER was recorded Each eye was again stimulated separatel and the was carefully covered Further VERs were then recorded with reverse pattern stim all normal subjects Our method and results of VER stud es will be presented elsewh

ERGs were recorded from infraorbital skin electrodes with the ps lateral earlo reference and the usual EEG electrodes at the vertex as the ground ones Chlorid disc electrodes 10 mm in diameter were attached by an adhesive ring to the lower li the centre of the pupil close to the lid margin and the contact was conf electrode paste

The primary amplification and recording of ERG was performed on a Elema Siemens EEG-machine (Mingograph Universal) time constant 0.3 sec frequency cut off from 70 Hz From the Mingograph the ampl fied s gnals were tr to a 2-channel 1000 points signal analyser averager (Hewlett Packard 5480) T responses with 200 mseconds averaging time were documented by means of photographs from the face of the oscilloscope of the signal averager For mo recording an XY recorder may be used

a similar procedure one female patient with an enucleated left eye was examined to ... whether the electrical field of the healthy right eye extended to the opposite lower lid

... o of the normal subjects both corneal and lower lid ERGs were recorded with four ... nt intensities of light (0 0025 0 01 0 04 and 0 2 joule respectively) averaging the ... es to 10 flashes at 15-second intervals after pre-adaptation to compare the waveform ... ations Corneal ERGs were recorded from Lovac contact lens electrode (Medical ... op Holland)

Results

latencies of the a wave and b-wave were manually measured from the ... lus-on to the peaks of the waves The amplitude of the photopic b-wave was ... ared from the peak of the a wave There were more interindividual variations ... plitudes than in latencies Usually the two eyes of one subject showed quite ... ir amplitudes although interindividual variations were great The results in ... al subjects are given in Table I and one example of normal corneal and lower ... RGs with four different intensities of light is presented in Fig 1 In the lower ... rves the sensitivity was five times that of the corneal curves and respectively ... ackground noise was greater in non-corneal ERGs but the waveform and time ... ions were similar Our technique with only 10 flashes at 15-second intervals or ... lashes at 2 Hz frequency revealed no measurable ERG from the lower lid ... rode of the enucleated left eye when the healthy right eye was stimulated In ... 2 there are curves from the lower lid electrode of the healthy right eye and the ... leated left eye with stimulation by 128 flashes at 2 Hz frequency and the ... itivity was twice that of the usual non-corneal recordings There are some ... ps in the curve from the lower lid of the enucleated left eye but they do not ... ntly differ from the background noise curves recorded from the two eyes ... stimulation by 10 flashes at 15-second intervals while both eyes were carefully ... red and the patient did not perceive any light so that it could not be ... rpreted *that the electrical field of the healthy right eye extended to the opposite* ... er lid When the right eye was carefully covered no ERG response of course ... recorded from the right lower lid electrode while the left enucleated eye was ... ng stimulated by 32 flashes at 2 Hz but when the right eye was purposely poorly ... ered with the patch there was an ERG with a large amplitude and long latency ... ave without an a wave showing characteristics of a dark adapted ERG with ... mulation by dim light (Fig 3)

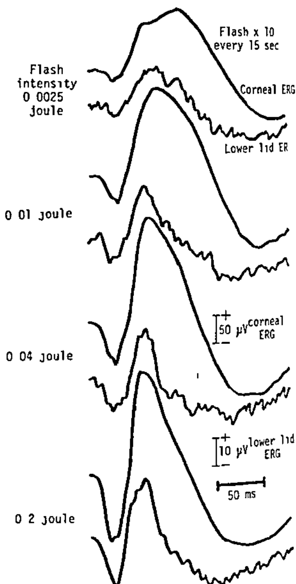


Fig 1

Corneal and non corneal ERGs in one normal subject examined with 10 flashes at intervals using four different flash intensities Note the difference in calibration

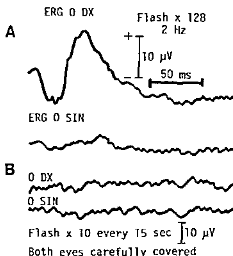


Fig 2

timulation of the right healthy eye with 128 flashes at 2 Hz frequency No measurable -onse from the infraorbital electrode of the left enucleated eye B The background noise -s from the two eyes with 10 flashes at 15 second intervals while both eyes were carefully red and the patient did not perceive any light Note the difference in calibration signals

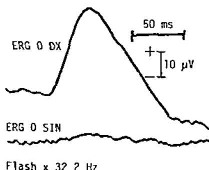


Fig 3

te right healthy eye was purposely poorly patched during the stimulation with 32 flashes at Hz frequency From the right infraorbital electrode there is an ERG with no a wa e and th a long latency and large amplitude b-wave characteristics of a dark adapted ERG with mulation by dim light No measurable response from the infraorbital electrode of the left enucleated eye

Discussion

Tassy et al (1968) examined the electrical field of the eye and found responses from the orbitoinferior skin electrode referred to the temple of the side They reported that with averaging technique (150 2100 responses) it is possible to record small responses from the corneal electrode of the opposite eye or from the skin electrodes around the opposite covered eye in one instance in one patient eviscerated eye The amplitude of the response at the cornea of the opposite eye was less than 1/50 of the normal ERG

Hirose & Jacobson (1968) reported their experience with simultaneous recording of ERG and VER in patients with visual disorders They used disc electrodes in diameter placed on the lower lid at the centre of the lower orbital margin referred to the joined earlobes Schmidt & Straub (1970) used small EEG-electrodes attached to the inner canthus of each eye and the reference electrode on the forehead The potentials registered by skin electrodes were 1/6 of the amplitude of the ERG in the conventional way They could record using 900 flashes small ERG from the electrode on the lower lid of an enucleated eye and thus showed the electrical field of the stimulated eye extended to the opposite side

Harden & Pampiglione (1970) Harden et al (1973) and Harden ... described the use of a non corneal nasal bridge electrode when investigating ... and children with a combined procedure of simultaneous ERG VER and ... order to establish the level of suspected visual impairment They reported the amplitude of the response recorded from the cornea was 20 times greater than amplitude of the response from the nasal bridge electrode referred to the electrode on the scalp at the vertex Stephens et al (1971) reported that the ERG responses from their skin electrodes were 1/3 1/5 of that obtained with the contact ... electrode Noonan et al (1973) examined the influence of direction of gaze on human ERG recorded from periorbital electrodes and found that in all directions of gaze except for upward gaze the ERG components were higher in amplitude ... the inferior electrode Nakamura (1975 1978) examined the isopotential ... ERG and found that the ERG was widely distributed over the face The maximum of the scotopic *ERG was located on the lower lid where the amplitude* was one ... or one fourth of that obtained from the contact lens electrode Nakamura used linked earlobes as the common reference

Marmor (1976) had successfully recorded corneal ERGs in children under ... years of age without sedation but Jones & France (1978) preferred non-corneal inferior orbital ridge electrodes for ERG when investigating children and recording simultaneously VERs Berry (1976) found 16 repetitive flashes at one per second sufficient to obtain good non-corneal ERGs from the lower lid electrodes, referred to the electrode at the bony margin of the orbit behind the outer canthus I did

79) reported their studies on skin-electrode ERG in the closed-eye state active electrodes were placed on the nasal side of the lower orbital margin ...mi's position 3 1971) Gitrow Tyler et al (1978) found that the lower lid ...ode produced a larger signal than the nasal electrode even with medial g but it was associated with greater interindividual variation and that the ...ode at the medial canthus combined with medial viewing gave closest ...ation to the corneal ERG

... chose skin electrodes placed on the lower lid at the centre of the lower orbital ...n and referred them to the ipsilateral earlobe electrode Signal averaging ...ique of 10 flashes at 15-second intervals were sufficient to get good photopic from non-corneal electrodes This simplified method for clinical ERG ...ut any discomfort to the patient is especially useful for infants children and ...ive adult patients Combining the non-corneal ERG simultaneously with the and EEG we can get information about the level of suspected visual ...irment When flash VERs are examined separately from the two eyes the ...uacy of the cover is verified by the absence of an ERG from the covered eye It ...ssible to reduce the light intensity and lengthen the interval between flashes to ...cotopic ERGs The same technique the photopic results of which in normal ...cts are presented in this report have later been used for examining many ...rent groups of patients and we found it a reliable method in clinical practice ...nvestigating retinal function

References

...hi E & Chiba Y (1971) The clinical ERG detected with skin electrodes *Acta soc ophthal* ... *5* 1056–1061

...ington J C Tepas D I Kropfl W J & Hengst W H (1961) Summation of retinal ...entials *J opt Soc Amer 51* 877–886

...ington J C Gouras P Tepas D I & Gunkel R (1961) Detection of the electroretino...am in retinitis pigmentosa. *Exp Eye Res 1* 74–80

...y H (1976) Clinical electroretinography by the skin electrode and signal averaged ...ethod *Canad J Ophthal 11* 160–164

...ow Tyler J F Crews S J & Drasdo N (1978) Electroretinography with noncorneal and ...rneal electrodes *Invest Ophthal Vis Sci 17* 1124–1127

...den A & Pampiglione G (1970) Neurophysiological approach to disorders of vision ...ancet *I* 805–809

...den A Pampiglione G & Pichton Robinson N (1973) Electroretinogram and visual ...oked response in a form of neuronal lipidosis with diagnostic EEG features *J Neurol ...euro urg Psychiat 36* 61–67

...den A (1974) Non-corneal electroretinogram Parameters in normal children *Brit J ...phthal 58* 811–816

Hirose T & Jacobson J H (1968) Combined recording of the electroretinogram (E... visual evoked occipital response (VER) in lesions of the visual pathways In Sch... ed Advances in electrophysiology and pathology of the visual system. Proc 6th ... Symp pp 125–138 G Thieme Leipzig

Jacobson J H Stephens G & Suzuki T (1962) Computer analysis of the ERG ... *(Kbh)* *40* 313–319

Jacobson J H Uchida S & Masuda Y (1966) Non-corneal electrodes for clinical ele... nography Proc 4th ISCERG Symp *Jap J Ophthal Suppl 10* 904–911

Jones R M & France T D (1978) Recording ERGs and VERs from unsedated ch... *Pediat Ophthal 14* 316–319

Marmor M F (1976) Corneal electroretinograms in children without sedation *J* ... *Ophthal 13* 112–116

Motokawa K & Mita T (1942) Über eine einfachere Untersuchungsmethode und ... schaften der Aktionstrome der Netzhaut des Menschen *Tohoku J Exp Med* ...

Nagata M & Jacobson J H (1966) Combined ERG and occipital response record... Burian H M & Jacobson J H eds Clinical electroretinography Proc 3rd IS... Symp pp 235–248 Pergamon Press London

Nakamura Z (1975) Clinical electroretinography from the skin *Acta Soc ophthal* ... 42–49

Nakamura Z (1978) Human electroretinogram with skin electrode Potential distrib... photopic and scotopic components *Jap J ophthal 22* 101–113

Noonan B D Wilkus R J Chatrian G E & Letuch E (1973) The influence of direc... gaze on the human electroretinogram recorded from periorbital electrodes ... utilizing a summating technique *Electroenceph clin Neurophysiol 35* 495–502

Schmidt B & Straub W (1970) Anwendung eines Elektronenrechners in der ... Elektroretinographie *Klin Mbl Augenheilk 156* 808–820

Stephens G M Inomata K Cinotti A Kiebel G & Maney I (1971) Canthus skin ... method with corneal displacement *Vis Res 11* 1213

Tassy A F Jayle G E & Graveline J (1968) Computer techniques in clinical ... (averaging) In Francois J ed The clinical value of electroretinography ... Karger Basel

Tepas D I & Armington J C (1962) Electroretinograms from noncorneal electrodes ... *Ophthal 1* 784–786

Uchida K Mitsuyu Tsuboi M & Honda Y (1979) Studies on skin-electrode ERG ... closed-eye state *J Pediat Ophthal 16* 62–65

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...RBONIC ANHYDRASE ISOENZYME C IN THE HUMAN RETINA

An immunohistochemical study

BY

TIMO KUMPULAINEN

The occurrence of carbonic anhydrase isoenzymes C and B in the retina of the human eye was examined with specific antisera against these enzymes Immunological analyses were carried out by the double diffusion method of Ouchterlony and the localization of the enzymes was studied by an application of immunoperoxidase (PAP) technique A large amount of isoenzyme C was detected in tissue sections from the human retina whereas the isoenzyme B was totally absent Isoenzyme C was considered to be located primarily in the glial elements of the retina correlating with the earlier findings obtained by traditional metal salt methods

Key words human retina – carbonic anhydrase – isoenzyme C – immunohistochemistry

...bonic anhydrase (CA) which catalyses the reversible hydration of carbon ...xide to carbonic acid occurs in mammals in two forms with different activities ...e so called *high activity CA is designated isoenzyme C and the low activity form* ...nzyme B The proportions and functional significances of these CA isoenzymes ...various tissues are not fully known (see e g Carter 1972) The ratio of isoenzyme ...to isoenzyme B in human erythrocytes is about 1 5 7 but it is not possible to ...fine the role of the B enzyme whereas the C enzyme is known to be responsible ...r vital respiratory functions (Chapman & Maren 1978)

...ceived November 5th 1979

CA activity has also been reported in various parts of the eye The histoche location of the enzyme in the pigment epithelium and glial elements of the (Korhonen & Korhonen 1965 Leder 1966 Bhattacherjee 1971 Musser & 1973a b) suggests a role in carbon dioxide metabolism and ionic changes p involved in the propagation of the nerve stimuli The histochemical met Hausler (1958) and Hansson (1967) are those most commonly used fo demonstration of CA activity in the retina These methods are based deposition of metal salts at the sites of enzyme activity but their specificity has been criticized (see Muther 1972 Churg 1973) Since immunological m seem to offer a highly specific means of demonstrating enzymes and m isoenzymes immunohistochemical methods have been developed for hum isoenzymes C (HCA C) and B (HCA B) as reported previously Korhonen 1978 Kumpulainen 1979) The immunoperoxidase method used also for the demonstration of CA in certain tissues of the rat and the (Delaunoy et al 1977 Roussel et al 1979 Spicer et al 1979) There is no p immunohistochemical study of this enzyme in the ocular tissues The aim present *investigation was to study the occurrence* of the CA isoenzymes in th of human eye

Material and Methods

Tissue samples

Three normal human eyes enucleated originally about 1½ hours post mort corneal transplantation were obtained from the Department of Ophthal Oulu University Central Hospital The eyes had been stored in cold physi saline solution for about three h before being transferred into liquid n Tissue pieces from ocular operations were also tested but the retinal ti immunoperoxidase staining procedure was found to be better preserved intact bulbus instead of a tissue piece was frozen before cutting with a micro

The retinal material for immunodiffusion was obtained by cutting a frozen sections of about 20 μ from the posterior part of the bulbus In thes thick sections the retina including the pigment cell layer usually loosened f choroid and was easy to collect into dry test tubes where it was allowed to t tissue fluid then being used for immunodiffusion

Antisera

Rabbit antisera against HCA C and HCA B were used for demonstratio isoenzymes Rabbit antiserum to ovalbumin served as a control serum immunohistochemical staining The preparation of the antisera together for their specificities is reported elsewhere (Kumpulainen 1979)

¬ological analyses

=double diffusion method of Ouchterlony (1968) on agarose plates with ¬ lbarbiturate buffer pH 8 6 ionic strenght 0 1 was used to test the immunore ies of the antisera and to demonstrate CA isoenzymes in the retinal material t o in the human erythrocyte hemolysate which served as a control sample ¬ining both CA isoenzymes Human erythrocyte hemolysate was prepared by olyzing the erythrocytes with an equal volume of distilled water

nohistological technique

¬mmunoperoxidase staining procedure for human CA has been discribed in l previously (Kumpulainen 19¬9) Frozen sections of about 11 μ were used for inohistochemical demonstration of the CA isoenzymes in the retina These ons were placed on cold glass slides and fixed with –10 C methanol (99%) ¬e removal from the cryostat chamber

the immunoperoxidase method the tissue sections were first incubated with bovine serum albumin (Sigma) in PBS (0 85% saline 0 01 M phosphate buffer 7 ?) for 5 min to minimize any unspecific absorbtion of the antisera Specific it anti HCA C and anti HCA B sera (in control rabbit anti-ovalbumin serum) ed 1 200 in PBS were then applied to slides for 15 30 min in a moist chamber slides were then washed for 30 min in PBS with rotatory agitation and bated for 15 30 min with swine anti rabbit serum IgG (Dako-immunoglobulins) ted 1 20 in PBS After a further washing for 30 min in PBS the slides were ibated with peroxidase anti peroxidase (PAP) complex (Dako immunoglobulins) ted 1 100 in PBS They were then washed again in PBS for 15 min before tment with 3 3 -diaminobenzidine (DAB Fluka 90 mg DAB/150 ml PBS plus drops of 3% H_2O_2) for 5 min Finally they were rinsed in distilled water ¬unted in glycerol and sealed with cover slips

¬he slides were examined with a Leitz Orthoplan microscope and photographed ¬ a Leitz Orthomat camera They were then rinsed in distilled water to remove cover slips and glycerol and new photomicrographs were taken after routine ¬natoxyline staining for demonstration of the different retinal layers

Results

bbit anti HCA serum generated a single clearly visible precipitation line with the inal tissue fluid in the doublediffusion analysis whereas no precipitation line was served between this and the anti HCA B serum The intensity of the precipitation es between human erythrocyte hemolysate and antisera to both isoenzymes were

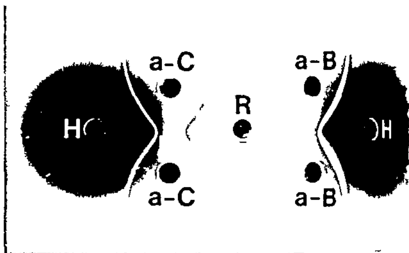


Fig 1

Immunodiffusion Well R contained 12 µl of human retinal tissue fluid and the wells of human erythrocyte hemolysate The wells a C were filled with 12 µl of rabbit anti serum undiluted (upper) or diluted 1 2 (lower) and the wells a B with 12 µl of anti HCA B serum undiluted (upper) or diluted 1 2 (lower)



Fig 2

Immunodiffusion All centre wells contained 12 µl of undiluted swine anti rabbit solution The peripheral wells were filled with 12 µl of rabbit anti HCA C serum (a-C) on the left 12 µl of rabbit anti HCA B serum (a B) in the centre and 12 µl of rabbit anti-ova serum (a OV) on the right diluted 1) 1 20 2) 1 40 3) 1 80 4) 1 160 5) 1 320

~~rable to the proportions of the isoenzymes in human erythrocytes (Fig 1) ioreactivities between the rabbit antisera and swine anti rabbit IgG were by immunodiffusion prior to their use for the immunoperoxidase procedure rabbit anti HCA B and anti-ovalbumin sera showed precipitation lines at ns double those required for the rabbit anti HCA C serum (Fig 2) which es that the IgG titres in the diluted anti HCA B and anti-ovalbumin sera were comparable with that of the anti HCA C serum When the retinal sections eated with the anti HCA C serum in the first step of the immunoperoxidase ure a strong peroxidase reaction was seen in the retina (Fig 3) while s treated with the anti HCA B (Fig 4) or anti-ovalbumin sera were negative t like staining of the main part of the retina after the immunoperoxidase lure with anti HCA C serum corresponds to the reticular arrangement of the bres A positive reaction was observed only in the inner segment of the or cell layer whereas the outer segment remained unstained There was only reaction in the ganglion cell layer while the intense colour of the pigment yer prevented visualization of the enzymes The retinal layers in the noperoxidase stained sections were identified after staining of the nuclei with oxyline (Fig 5 and 6)

Discussion

raditional histochemical methods show CA activity in the retina of albino rats nice to be located in the pigment epithelium and Muller cells (Korhonen & onen 1965 Leder 1966) and similar findings have been obtained with other ls (Bhattacherjee 1971 Musser & Rosen 1973a)

the primate retina the cones (but not the rods) exhibited CA activity in on to the Muller cells by the method of Hansson In the pigment epithelium rarance was obscured by pigment granules (Musser & Rosen 1973b)

present results demonstrate the occurrence of the high activity type isoenzyme ie retina of the human eye principally in the glial elements and that part of ptor cell layer which contains the inner segments of the rods and cones

role of isoenzyme C may be similar to that probably fulfilled by CA in brain r CA has been localized in the glial cells of the mouse brain while the neuron lack this enzyme (Korhonen et al 1964) Later immunohistochemical investiga support this finding (Delaunoy et al 1977 Roussel et al 1979 Spicer et al) It is suggested that in the nervous tissue carbon dioxide formed in the ons diffuses into the glial cells where it is converted to bicarbonate by CA ysis CA also influences the sodium and potassium equilibrium of neuronal ents (see Korhonen et al 1964 Carter 1972) and may thus have an effect on

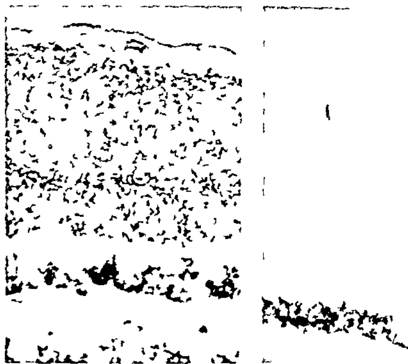
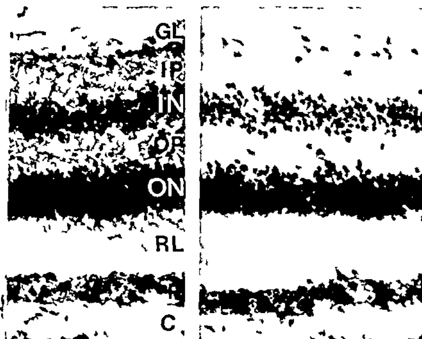


Fig 3

Figs 3 and 4

Human retina after staining by the immunoperoxidase method using the rabbit anti serum in Fig 3 and rabbit anti HCA B serum in Fig 4 X 180

the propagation of nerve stimuli CA is generally regarded as a cytoplasmic enzyme being readily soluble after cell disruption (see Lindskog et al 1971) The considerable amount of HCA C which appeared in the soluble portion of the retinal tissue after thawing suggests that there is no substantial binding to the subcellular structures HCA B was not detected in the retinal tissue fluid using the immunodiffusion method This may mean that this enzyme may be more tightly bound to the other material but in such a case it should still give a positive reaction in the immunohistochemical staining The lack of HCA B in immunodiffusion also indicates that there was no contamination with blood Methanol and other alcohol fixatives are often employed in immunohistochemistry as they often preserve at least a part of the antigenicity of the enzyme proteins (see Sternberger 1974) Although the morphology would be better preserved with aldehyde fixation methanol was



Fip 6

Figs 5 and 6

ections as in Figs 3 and 4 after staining with hematoxylline for demonstration of the layers GL layer of ganglion cells and optic nerve fibres IP inner plexiform layer ter plexiform layer ON outer nuclear layer RL recptor cell layer P pigment cell layer C choroid X 180

as a fixative instead of aldehydes because preliminary observation had shown ldehydes destroy the antigenicity of HCA C Attempts were also made here to nstrate HCA C in other parts of the eye Better fixation methods are required ver before an accurate immunohistochemical demonstration of CA in the is ciliare and in the endothelium of the human cornea for instance is possible ervation of the antigenicity of animal CA appears to be better because unohistochemical studies on animal CA in aldehyde fixed and paraffin embed material (except ocular tissues) have been reported (Delaunoy et al 1977 sel et al 1979 Spicer et al 1979) and therefore immunohistochemical ization of CA in the eyes of certain albino animals has been subjected to further ination

n a pour en

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References

Bhattacherjee P (1971) Distribution of carbonic anhydrase in the rabbit eye a dem histochemically Exp Eye Res 12 356 359

Carter M J (1971) Carbonic anhydrase isoenzymes properties distribution and significance Biol Rev 47 465–513

Chapman S K & Maren T H (19 8) A search for the function of human anhydrase B Biochim Biophys Acta 527 272 2 6

Churg A (1973) Carbonic anhydrase histochemistry evidence for non-enzymatic and artifact production Histochemie 36 293 301

Delaunoy J P Roussel G & Mandel P (19) Localisation immunohisto anhydrase carbonique forme C dans le système nerveux central du Rat C R (Paris) 285 801 804

Hansson H P J (1967) Histochemical demonstration of carbonic anhydrase Histochemie 11 112 128

Hausler G (1958) Zur Technik und Spezifität des histochemischen Carboanhydrase im Modellversuch und in Gewebsschnitten von Rattennieren Histochemie 1 29

Korhonen L K Naatanen E & Hyyppa M (1964) A histochemical study of anhydrase in some parts of the mouse brain Acta Histochem 18 336 34

Korhonen E & Korhonen L K (1965) Histochemical demonstration of carbonic activity in the eyes of rat and mouse Acta ophthal (Kbh) 43 4 5 48

Kumpulainen T & Korhonen L K (19 8) Immunohistochemical demonstration anhydrase Histochem 58 183 192

Kumpulainen T (19 9) Immunohistochemical localization of human carbonic isoenzyme C Histochemistry 62 271 280

Leder O (1966) Die Verteilung von Carboanhydrase im Rattenauge 331–336

Lindskog S Henderson L E Kannan K K Liljas A Nyman P O & Strandberg Carbonic anhydrase In Boyer P D ed The enzymes Vol 5 3rd ed Academic Press New York

Musser G L & Rosen S (1973a) Localization of carbonic anhydrase activity in retina Exp Eye Res 15 105 119

Musser G L & Rosen S (1973b) Carbonic anhydrase activity in primate photorecep Eye Res 15 467 470

Muther T F (19 2) A critical evaluation of the histochemical methods for anhydrase J Histochem Cytochem 20 319 330

Ouchterlony O (1968) Handbook of immunodiffusion and immunoelectrophor Arbor Science Publ Ann Arbor

G Delaunoy J P Nussbaum J L & Mandel P (1979) Demonstration of a specific ...ation of carbonic anhydrase C in the glial cells of the rat CNS by an immunohistochemi...
...thod B ain Res 160 47–55
...rger L A (1974) Immunocytochemistry Prentice Hall Inc Englewood Cliffs New ...
... S Stoward P J & Tashian R E (1979) The immunohistolocalizat on of carbonic ...drase in rodent tissues J Histochem Cytochem 27 820–831

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HISTOCOMPATIBILITY (HLA) ANTIGENS IN CAPSULAR GLAUCOMA AND SIMPLEX GLAUCOMA

BY

ESKIL OLIVIUS and WERNER POLLAND

HLA antigen typing of 39 patients with capsular glaucoma and 40 with simplex glaucoma showed a significantly higher frequency of Bw35 in the capsular glaucoma group compared to a control group of 985 blood donors. In the simplex glaucoma group Bw35 was less frequent and the difference not significant.

Key words capsular glaucoma – simplex glaucoma – HLA antigen.

During recent years there has been an extensive search for associations be- antigens of the major human histocompatibility antigen system (HLA-syst- specific diseases and several eye diseases have been shown to be correlated w- HLA antigens (reviewed by Rahi (1979)). Patients with open angle glauco- reported to have significantly more HLA B7 and B12 and it has been su- that occurrence of these antigens is an indicator of the development of visual loss (Shin et al. 1977). Aviner et al. (1976) found that Bw35 was more fre- among patients with open angle glaucoma in a material from New York against 23% in a control series.

On the contrary Damgaard Jensen & Kissmeyer Nielsen (1978) could not firm these observations in a Danish material. They found no significant diff- from a large control series. Bw35 was present in 10% of the open angle gla-

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s against 13% of the control group and B7 and B12 also had frequencies iat of the control group Rich et al (1978) found no significant difference n glaucomatous and control populations in incidences of B7 B12 Bw35 A3 11 Kass et al (1978) found in one white population with primary open angle ma a significant decrease in HLA A1 and a significant increase in antigen nation HLA B7 and Bw22 These differences could not be confirmed in a l white population with primary open angle glaucoma and they suggested ssociations of A and B loci of the HLA antigen system and primary ingle glaucoma may arise by chance or may be true only in certain ethnic s David et al (1979) found no differences with regard to the frequencies of A antigens and groups of open angle glaucoma and ocular hypertension tively

aim of the present study was to compare the occurrence of HLA antigens in lar glaucoma and simplex glaucoma respectively to a control group of the region

Material and Methods

ity nine patients with typical open angle glaucoma were selected forty of them simplex glaucoma in one or both eyes and thirty nine capsular glaucoma The ria of glaucoma were pathological high intra-ocular pressure (more than 30 without therapy) together with typical glaucomatous disc cupping and visual s with characteristic glaucomatous defects The patients of the investigation selected before their HLA antigens were known. The patients went through compatibility antigen typing by lymphocyte microcytotoxicity technique The rol group consisted of 985 blood donors They were tested with the same era at the same laboratory Department of Blood Center University of Umea he differences between the groups were statistically tested with the chi-square To compensate for the large number of antigens tested (15) the P value was rected by multiplication with 15

Results

frequencies of 15 HLA antigens tests are presented for the simplex glaucoma up (Table I) and the capsular glaucoma patients (Table II) A significant higher quency of Bw35 was found in the capsular glaucoma group 28% compared to in the control group ($P < 0.0075$) In the simplex glaucoma group there was Bw35 which did not deviate significantly from the control group In addition y slight deviations were found (Table I & II)

Table I

The frequencies of different HLA antigens in a group of patients with simple (n=40) and in the control group (n=985)

HLA antigens	No of subjects with antigens	%	Control group	%	P	cr
A1	8	20%		19%		
A2	25	63%		58%		
A3	15	38%		31%		
A9	5	13%		16%		
A11	4	10%		13%		
Aw26	5	13%		12%		
B5	1	3%		13%	<0.05	
B7	11	28%		36%		
B8	9	23%		18%		
B12	16	40%		°8%		
Bw15	10	25%		°5%		
Bw22	2	5%		4%		
Bw27	4	10%		16%		
Bw35	7	18%		9%		
Bw40	8	20%		19%		

Table II

The frequencies of different HLA antigens in a group of patients with capsular (n=39) and in the control group (n=985)

HLA antigens	No of subjects with antigens	%	Control group	%	P	a
A1	5	13%		19%		
A2	26	67%		58%		
A3	6	15%		31%	<0.05	
A9	12	31%		16%	<0.05	
A11	2	5%		13%		
Aw26	4	10%		12%		
B5	6	15%		13%		
B7	8	21%		36%		
B8	5	13%		18%		
B12	11	29%		°8%		
Bw15	7	18%		°5%		
Bw22	1	3%		4%		
Bw27	6	15%		16%	<0.001	<
Bw35	11	28%		9%		
Bw40	10	26%		19%		

Discussion

are several problems and sources of error when studying the frequencies of ...gnes Racial stratification of the population statistical errors and selec... patients after HLA typing might be mentioned We have tried to avoid these ... by selecting the patients before HLA typing and the patients and the ...l group live in the same geographical area The control group however is ...er than the glaucoma patients It is not known if this might affect the results ...cific Bw35 sera was not available mixed sera of B5 and Bw35 was used If ...5 is found in B locus Bw35 can exist together with B5 and not be discovered a false low incidens of Bw35 might have been found but this possible ...estimation of Bw35 is probably the same in all three groups and will not affect ...nclusion

...his study we have found a significant deviation of HLA Bw35 which was more ...ently represented in the capsular glaucoma group than in the control group ...nplex glaucoma Avner et al (1976) found higher frequency of HLA Bw35 ...so found a higher frequency (18% against 9% in the control group) but this ...ence was not significant perhaps due to a smaller material However most ...its with capsular glaucoma do not have the Bw35 thus the connection between ...tigen and the disease is weak.

...e great variation between the reports of connection between open angle ...oma and specific HLA antigens might depend on different criteria for the ...osis of glaucoma In this investigation we have endeavoured to include only ...oma with typical glaucomatous damage doubtful cases were excluded before ...LA typing

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...uthors thank Dr Lena Wahlby Department of Blood Center University of Umeå for ...ssistance with HLA typing

References

...r Z Henley W L Founo M & Leopold I H (1976) Histocompatibility (HLA) ...igens and primary open angle glaucoma *Tissue Antigens* 7 193–200

...aard Jensen L & Kissmeyer Nielsen F (1978) HLA histocompatibility antigens in ...n angle glaucoma *Acta Ophthal* 56 384–388

... R Mayer C Baumgarten I & Abrahams C (1979) HLA antigens in glaucoma and ...lar hypertension *Brit J Ophthal* 63 293–296

Kass M A Palmberg P Becker B & Miller J P (1978) Histocompatibility ... open angle glaucoma *Arch Ophthal (Chicago)* 96 2207–2208

Rahi A H S (1979) HLA and eye disease *Brit J Ophthal* 63 283–292

Ritch R Podos S M Henley W Moss A Southren A L & Fotino M ... association of histocompatibility antigens with primary open angle glaucoma ... *(Chicago)* 96 2204–2206

Shin D H Becker B Waltman S R Palmberg P F & Bell C E (19..) The prevalence ... HLA B12 and HLA B7 antigens in primary open angle glaucoma *Arch Ophthal* ... 95 224–225

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LYMPHOCYTE SUBPOPULATIONS IN PERIPHERAL BLOOD AND CEREBROSPINAL FLUID FROM PATIENTS WITH ACUTE OPTIC NEURITIS

BY

HARALD NYLAND[1], ARE NÆSS[2] and JON ERIK SLAGSVOLD[3]

Ten patients with acute optic neuritis (AON) were examined for T and B lymphocytes in blood and cerebrospinal fluid by means of rosette techniques. The percentage of T lymphocytes in blood was significantly decreased (54±3%) compared to controls (66±2%). Absolute numbers of T lymphocytes and relative and absolute B lymphocyte concentrations were not significantly different from controls. The cerebrospinal fluid (CSF) T lymphocyte percentage was significantly increased (88.8% compared to 78.0% in controls). The relative CSF immunoglobulin G concentration was elevated in four patients (40%). On agarose gel electrophoresis bands in the gamma globulin region were found in two patients (20%).

Key words: optic neuritis – cerebrospinal fluid – peripheral blood – lymphocyte subpopulations.

e optic neuritis (AON) is the initial symptom in 10-20% of patients with ple sclerosis (MS) (Leibowitz et al. 1966). In adults most cases of AON are festations of MS (Taub & Rucker 1954; Hutchinson 1976). Immunological anisms have been suggested to be a factor in the etiology of both disorders emata et al. 1977; Perkin 1979).

o recent reports suggest disturbances in the distribution of B and T lymphocy blood and cerebrospinal fluid (CSF) from patients with AON (Kam-Hansen et 978; Traugott 1978). We have earlier demonstrated changes in lymphocyte opulations in blood and CSF from patients with active MS (Næss & Nyland). The present paper reports the results of investigations on lymphocyte opulations in blood and CSF from patients with AON compared to patients active MS and controls.

ved October 24th, 1979.

Materials

Patients

Group 1 consisted of 10 patients with AON admitted to the Department of Ophthalmology 2 males and 8 females aged between 18 and 51 (mean ...). The diagnosis was based on medical history and clinical investigations (including visual acuity visual fields and color vision) The neuritis was retrobulbar ... and intraocular (papillitis) in 3 cases Two patients had an earlier episode of neuritis The affection was bilateral in 3 and unilateral in 7 patients ... neurological and neuroradiological examinations were performed in 2 p... Patients with additional clinical features suggesting MS were excluded from ... group

Group 2 consisted of 21 patients with active MS (Næss & Nyland 197...) ... to the Department of Neurology 8 males and 13 females aged between ... (mean 36) years Fifteen of the patients had a history of visual disturbances

Controls

For peripheral blood studies 30 healthy persons were selected from ... hospital staff For CSF examinations 17 patients with headache and psychoneurotic disorders admitted to the Department of Neurology were ... as controls No organic cause for the complaints were found and the ... counts protein and IgG concentrations were normal

Blood samples from 7 AON patients were obtained within 2 weeks (mean ...) of the acute visual blur Blood from the other 3 patients were examined a... and 52 days respectively Two patients were on corticosteroid treatment w... samples were obtained

CSF was obtained by lumbar puncture within 2 weeks of the onset of ... from 10 of the patients with AON and from 17 MS patients d... exacerbation

Methods

Lymphocyte studies

Peripheral blood lymphocytes Blood was obtained by venipuncture and immediately ... ted by glass beads 3 ml of defibrinated blood was mixed with an equal ... physiological saline and carefully layered on 3 ml of Lymphoprep® (Nyegaard & Co ...) a plastic tube centrifuged for 40 min at room temperature at exactly 400 g at the ... between blood saline and Lymphoprep® The cells from the interface were carefully ... off and washed 3 times in hanks balanced salt solution (HBSS) and the concentration adjusted to 4×10^6 ml Monocyte contamination as judged by la ex particle ... usually 5-10%

ocytes 0.25 ml of the lymphocyte suspension was mixed with 0.25 ml of 0.5% sheep cytes in HBSS. The mixture was incubated at 37 C for 5 min, centrifuged and stored ater overnight. The supernatant was then removed and a drop of 0.6% glutaraldehy d to the cells. After incubation in ice water for 20 min the cells were resuspended op of the suspension was placed on a glass slide and covered with a coverslip. A um of 200 lymphocytes were counted at a magnification of 600 x. Lymphocytes more than 3 sheep erythrocytes were counted as rosette forming cells (Næss & 119 8)

hocytes Receptors for the Fc portion of immunoglobulin G were used as marker for B Indicator cells (EA) were prepared by sensitizing ox erythrocytes (E) with one inating unit of rabbit IgG antibodies (A). 0.25 ml of the lymphocyte suspension ning 10^6 lymphocytes was mixed with 0.25 ml of indicator cells (EA). The mixture was ited at room temperature for 15 min, stored at 4 C overnight and counted as for E s (Christensen et al 1977)

mphocytes The total number of lymphocytes/ml was determined in a Fuchs-Rosenthal ing chamber by counting the cells in the first and the last portion of the fluid sample ount of 0-5 cells/ml were accepted as normal. Enumeration of T lymphocytes in CSF was rmed as described by Næss (1976). Briefly, 3 ml of CSF were allowed to drop from the dla nto a plastic tube containing 6 ml of HBSS. The tube was centrifuged at 400 C for 40 at room temperature. The supernatant was then removed and 0.07 ml of sheep rocytes suspended in HBSS to 0.5% were added. Incubation, recentrifugation and the an ng steps of the technique were then performed as described above for peripheral d lymphocytes. Because of the low numbers of lymphocytes present in the CSF from ents with AON, tests for Fc receptor bearing cells in the CSF could not be included
he CSF immunoglobulin G (IgG) were quantitated by single radial immunodiffusion g commercial plates (Behringwerke AG, Marburg Lahn, West Germany). The normal entration ranges given for CSF IgG are 8-40 mg/l. The CSF protein concentrations were nated by the modified Folin Ciocalteau method described by Schackerle & Pollack 3). The upper normal value for CSF protein is 0.5 g/l
grose gel electrophoresis was performed on CSF concentrated x 50 using Amicon centrator B 15 (Amicon Corp, Lexington, Mass, USA). The samples were inspected for oclonal bands in the gamma area.

tt Percentages and concentrations are given as mean value ± standard error of mean). The significance of the data was established by the use of Student's *t* test (two tailed) for blood examinations by Wilcoxon test for the CSF

Results

pheral blood. The mean lymphocyte numbers in peripheral blood from patients h AON was 2697 cells/ml, slightly higher than in the controls (209? cells/ml =0.018) while the MS patients had 2166 cells/ml

mphocytes The percentage of T lymphocytes was significantly reduced (?1±° /

Table I
Total and relative T lymphocytes in peripheral blood from patients with ac[illegible]

Croup	No of patients	Lymphocytes ml	T lymphocytes %	Th[illegible]
Acute optic neuritis	10	2697±248[1]	54+3[2]	[illegible]
Active multiple sclerosis	21	2166±264	47+3[3]	[illegible]
Controls	30	2095±114	66+2	[illegible]

[1] = $P = 0.018$ [2] = $P = 0.005$ [3] = $P < = 0.0005$ [4] = P 0.003

$P=0.005$) in patients with AON when compared to the control group (Ta[illegible] However the absolute numbers were slightly increased companred to the co[illegible] Patients with active MS showed a decrease in both relative and absolute number[illegible] T lymphocytes (Table I)

B lymphocytes Both the relative and absolute numbers of B lymphocytes were [illegible] but not significantly increased in patients wint AON This increase was not marked as that observed in patients with active MS (Table II)

CSF lymphocytes The CSF samples from 2 out of 10 AON patients and 11 o[illegible] MS patients had a lymphocytic pleocytosis The CSF T lymphocyte perce[illegible] could be determined in 4 AON patients and showed a significant increase (m[illegible] 88 8%) as compared to 78 0% in the control group (Table III) All MS patien[illegible] increased percentages of CSF T lymphocytes ranging from 89-96% (mean 9[illegible]

Table II
Total and relative numbers of B lymphocytes in peripheral blood from patients with acute optic neuritis

Group	No of patients	B Lymphocytes %	B lymphocytes ml
Acute optic neuritis	10	32±3	94+134
Active multiple sclerosis	21	39±3[1]	1089[2]
Controls	30	26+2	580+43

[1] $P < 0005$ [2] P 0 003

Table III
T lymphocytes in CSF from patients with AON and MS

Group	No of patients	T lymphocytes % mean (range)
Acute optic neuritis	4	88 8 (87 9?)*
Active multiple sclerosis	17	9? 8 (89-96)
Controls	17	78 0 (55-89)

* $P = 0\ 002$ (Wilcoxon test) ** $P <= 0\ 0005$ (Wilcoxon test)

oteins. In the 10 AON patients the total protein concentration was mean 0 51 nges 0 39 0 96) The mean IgG concentration was 4 2 mg/l (ranges 2 7 7 9) elative IgG concentrations was elevated above the upper normal value of in 4 patients Two patients had oligoclonal IgG bands in agrose gel phoresis

he 17 MS patients the total protein concentration was mean 0 75 g/l (ranges 66) Sixteen of the patients had a relative increase in the relative IgG ntrations The mean IgG concentration was 10 7 mg/l (ranges 5 9 23) Ten 12 patients examined with agrose gel electrophoresis had oligoclonal bands

Discussion

esent study compares the immunological findings in a group of patients with o that of group of patients with active MS

AON *patients* had a significant increase in peripheral blood lymphocytes as red to controls The relatice concentration of T lymphocytes decreased he absolute numbers were normal This finding is different from that in MS ts who have a significant decrease of both absolute and relative T lymphocyte ntrations (Næss & Nyland 1978) Recently it has further been shown that a of T lymphocyte the T suppressor cells also are decreased in active MS llestone & Oldstone 1979) These T cells have a suppressor activity on the B ocyte proliferation and differentiation *in vitro* We found slightly but not cant increased numbers of circulating B lymphocytes in patients with AON may suggest that humoral immunity is operative in the disease However al values have been reported for the serum concentration of immunoglobulins et al 1973) Abnormally high titres of measles antibodies have been found in from AON patients but the titres ar lower than in patients with MS (Perkin

The CSF samples from 2 AON patients (20%) and from 14 MS patien[ts] had a mononuclear pleocytosis Similar results have been reported ea[rlier] (Sand-berg & Bynke 1973 Perkin 1979) The T lymphocyte percentage was incr[eased in] AON (mean 92 8%) Traugott (1978) found a mean of 72% CSF T lympho[cytes in] 2 patients with AON compared to 80% in relapsing MS Normal values fo[r CSF T] Lymphocytes were not given but a control group of patients with [other] neurological diseases had T cell percentage of 65 in CSF In anoth[er study] Kam Hansen et al (1978) found 79 9% T cells in CSF from five AON [patients] compared to 88% in MS CSF This similarity in lymphocyte pattern in C[SF from] AON and MS patients is further reflected in a recent cytologic examinati[on] (Taskinen et al 1979) showing an identical abnormal cellular pattern in [both] conditions The CSF lymphocytes form part of the total pool of c[irculating] lymphocytes and the increased proportion of T lymphocytes may re[flect] selective crossing of the blood liquor barrier by the T cells

The CSF relative IgG concentration was above normal in 4 of 10 pa[tients with] AON (40%) while 16 of the 17 MS patients had elevated concentrations (9[4%) The] same differences were observed between the two groups of patients when [studied] by agrose gel electrophoresis Oligoclonal bands were present in CSF fro[m 40% of] the AON patients and 83% of the MS patients Our results correspond we[ll with] results published by Sandberg & Bynke (1973) The antibody specific[ity of the] oligoclonal IgG has not been determined but a small proportion seems to [be] measles antibodies (Link et al 1973) The occurrence of oligoclonal CSF [IgG in] patients with AON does not invariably predict a later development of MS ([Sandberg] & Bynke 1973)

In conclusion the limited work done on lymphocyte subpopulation[s] indicate changes in blood and CSF similar to those observed in patients [with] MS The demyelinating lesions are also similar but the degree of in[volvement is] more limited in patients with AON without additional clinical signs This [is] reflected in the lower incidence of elevated relative IgG concentra[tion and] oligoclonal IgG bands in CSF from AON patients

References

Christensen B E Jønsson V Matre R & Tønder O (1978) Traffic and localization of B lymphocytes in the normal human spleen Scand J Haemat 20 246–2[5]7

Huddlestone J R & Oldstone M B A (1979) T suppressor (T_g) lymphocytes [fluctuate in] parallel with changes in the clinical course of patients with multiple sclerosis [J Immunol] *123* 1615–1618

Hutchinson W M (1976) Acute optic neuritis and the prognosis for multiple [sclerosis J] *Neurol Neurosurg Psychiat* *39* 283–285

ınsen S Fryden A & Link H (1978) B and T lymphocytes in cerebrospinal fluid and in multiple sclereosis optic neuritis and mumps meningitis *Acta neurol Scand 58* 03
ıon B G (197?) Agarose electrophoresis *Scand J Clin Lab I est 29 Suppl 124*
tz U Alter M & Halpern L (1966) Clinical studies of multiple sclerosis in Israel 4 neuropathy and multiple sclerosis *Arch Neurol Psychiat (Chicago) 14* 459–466
Norrby E & Olsson J E (1973) Immunoglobulins and measles antibodies in optic us *New Engl J Med 289* 1103–1107
ne D (197?) Optic (retrobulbar) neuritis In McAlpine D Lumsden C E & Acheson (Eds) Multiple Sclerosis A Reappraisal pp 148–163 Churchill Livingstone ɔurgh
(19/6) Demonstration of T lymphocytes in cerebrospinal fluid *Scand J Immunol 5* 168
ı & Nyland H (1978) Multiple sclerosis T lymphocytes in cerebrospinal fluid and *l Eu Neu ol 17* 61 66
G D (19 9) Optic neuritis and multiple sclerosis An immunological comparioson ose F C (Ed) Clinical Neuroimmunology pp 31?–328 Blackwell Oxford
rg M & B nke H (1973) Cerebrospinal fluid in 25 cases of optic neuritis *Acta Neu ol 1 49* 443–452
terle G R & Pollack R L (1973) A simplified method for the quantitative assay of amounts of protein in biological material *Ann Bi chem 51* 654 657
en E Livanainen M Erkkila H Kovanen J & Raitta C (1979) Cerebrospinal fluid ytosis in patients with optic neuritis *Neurol gy 29* 538
R B & Rucker C W (1954) The relationship of retrobulbar neuritis to multiple osis *Amer J Ophthal 37* 494–497
ɔtt U (1978) T and B lymphocytes in the cerebrospinal fluid of various neurological ıses *J Neurol 219* 185–197

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A STUDY IN THE MEASUREMENT OF CORNEAL ENDOTHELIAL CELL DENSITY USING THE SPECULAR MICROSCOPE

BY

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Six subjects who never wore contact lenses underwent six determinations of corneal cell density using each of two measurement modes Mode A the eye was applanated once and pairs of photographs were taken Mode B the eye was applanated and a single photograph was taken For each measurement mode data were collected on two separate sessions (Test, Retest). Chi-square analyses revealed a significantly larger proportion of uncountable photographs from the first measurement session and analysis of variance revealed that Mode A was less reliable than Mode B upon retesting It was concluded that Mode B was the preferred measurement mode and that many more than six determinations be made on the initial session in order to obtain six readable photographs Finally estimates of inter and intra session variation, intra-pair variation and inter and intra-observer variation are given

Key words cornea – corneal endothelial cell density – specular microscope human cornea

Determination of endothelial cell density using the specular microscope has be[…] increasingly valuable in the study of effects of various medications [...] surgical procedures on the structure and function of the corneal endoth[…] (Binkhorst et al 1977 Hirst et al 1977) A variety of problems [...] encountered in the assessement of endothelial cell density using current te[…] and the need for evaluating sources of error has been emphasized by [...] investigators (Laule et al 1978 Binder 1978 Sperling & Gundersen 19[…])

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urpose of the present study is to identify and quantify sources of variability leasurement of endothelial cell density On the basis of these findings endations are made regarding the utilization of specular microscopy e especially as it relates to longitudinal prospective studies

Material and Methods

endothelial cell density (cells/mm²) was measured on a randomly selected each of six subjects (two females four males) All subjects had clinically corneas never wore contact lenses and had no history of ocular disease ibjects had the right eye measured and the other three subjects had the left sured

yber specular microscope was used to visualize the corneal endothelium micrographs were taken of the central corneal endothelium using the photographic attachment according to the method suggested with the ent (Syber 1972) Six specular micrographs of the study eye were obtained gle ophthalmologist (E M) using each of two measurement modes (Mode e B) For Mode A the photographs were taken pairwise i e the eye was ted once and a pair of photographs was taken For Mode B the photographs en independently i e the eye was applanated before each photograph was id then the dipping cone was removed from the corneal surface For each ment mode data were collected on two separate sessions (Test Retest) ere three days apart For each mode and each session the order in which the were measured was randomized

ard film processing technique was used to produce non identifiable proofs elial cells were counted by a single technician using the fixed frame method & Kaufman 1976) A counting overlay of 0 04 mm × 0 3 mm was chosen its dimension yielded the largest proportion of cells relative to the proof ion which could easily be counted Proofs were graded as Good countable clearly distinguishable Fair countable but some cells not clear Bad not le For some (approximately 10%) of the Fair proofs a smaller counting (0 04 mm × 0 2 mm) was used

the estimation of intra-observer variation a subset of photographs was I twice by the same technician This same subset was also counted by a technician for the purpose of assessing inter-observer variation Both ians utilized the same counting procedures

resulting data were analyzed statistically using chi square analysis with ning for trend (Maxwell 1971) and analysis of variance with repeated es (Afifi & Azen 1979)

Results

Table I summarizes the distribution of the readability (Good Fair Bad) of photographs per subject The proportion of Bad photographs was larger for the first session (Mode A Test) than that for each of the other sessions ($\chi_1^2 = 13.1$ $P < 0.005$) There was no significant difference in proportions of Bad photographs for sessions 2-4 (χ_2 0.5 NS) Fair photographs were randomly distributed throughout the measurement process

Table II summarizes for each subject and session the mean (+ SEM) cell density of the Good and Fair photographs Also shown in the table is the mean density for each subject (averaged over sessions) Analysis of variance (T) showed a considerable (although non significant) mean difference ([illegible] mm²) between Test and Retest for Mode A and a negligible mean difference (− 11 cells/mm²) for Mode B

Table IV presents for each mode estimates of intra and inter session standard deviations Modes A and B were equally variable within a session (F = 1.3 NS) Mode B was significantly less variable than Mode A upon retesting (F 5.06 P [illegible]) Also shown is the intra pair standard deviation for Mode A i e the analysis of pairs of photographs for those pairs that were graded Fair or Good Variability of cell density within pairs using Mode A was equivalent to that with n repeated Mode B (F − 1 07 NS)

Sixteen selected photos were counted twice by the same technician on separate occasions The mean difference in cell density was 5 cells mm² (NS) The same set of photos was counted by a second technician The difference in cell density was 117 cells/mm² (t 3 26 $P < 0.01$)

Table I
Summary of the Readability of Photographs by Session

Readability* of photographs per subject	Session 1 Mode A (Test)	Session 2 Mode B (Test)	Session 3 Mode A (Retest)	Session 4 Mode B (Retest)
Good	3	16	7	[illegible]
Fair	20	17	24	[illegible]
Bad	13	3	5	[illegible]
Proportion of Bad photographs	0 36	0 08	0 14	[illegible]

* Good = cells clearly distinguishable Fair = some cells not distinguishable Bad = not countable

Table II

Endothelial Cell Density (cells/mm²) Summary Statistics ($\bar{x} \pm$ SEM (n))

Session 1 Test (Mode A)	Session 2 Test (Mode B)	Session 3 Retest (Mode A)	Session 4 Retest (Mode B)	Average (weighted by n)
2882.2 ± 93.5 (5)	3082.1 ± 107.5 (6)	3193.2 ± 41.2 (6)	3123.8 ± 72.1 (4)	3074.2 ± 46.9 (21)
2763.3 ± 62.2 (6)	2759.6 ± 110.3 (4)	2948.8 ± 72.6 (5)	2799.1 ± 62.5 (5)	2817.9 ± 43.4 (20)
2853.0 ± 62.5 (4)	2957.2 ± 35.6 (6)	3061.7 ± 52.6 (6)	2839.6 ± 85.1 (6)	2934.7 ± 34.5 (22)
2748.9 ± 48.1 (3)	2818.3 ± 54.4 (6)	2948.8 ± 33.3 (5)	2679.5 ± 50.0 (6)	2798.9 ± 28.0 (20)
2471.2 ± 73.5 (3)	2415.7 ± 64.5 (6)	2415.7 ± 45.6 (5)	2457.4 ± 51.5 (6)	2436.5 ± 33.0 (20)
2374.1 ± 125.0 (2)	2349.1 ± 103.3 (5)	2353.2 ± 85.9 (4)	2415.7 ± 60.8 (6)	2376.5 ± 51.3 (17)

Discussion

ata from this study indicate that the measurement of endothelial cell density ig the specular microscope and measurement Mode B produces reliable upon retesting in normal subjects (Table III). Mode A on the other hand iown to be somewhat less reliable than Mode B upon retesting (Table III) igh the intra session variation was statistically equivalent to that using Mode B : IV). The non significant reduction in variation within pairs of measurements ipared to variation within replicates (167 cells/mm² vs 173 cells/mm², Table ay be attributed to slight movement in the cornea relative to the applanating during the recharging of the flash attachment to the Nikon photographic ment (average time for recharge = 5 seconds). The significantly larger rtion of unreadable photographs for the first session but not in the third n (both Mode A) suggests that there may be a learning effect on the part of bjects. The subjects did in fact exhibit some uneasiness during the initial rement session. We can only speculate that if Mode B had been the initial d used a similar pattern would have occurred.

ing the developmental stages of a proposal to study the effects of intra-ocular on the corneal endothelium utilizing specular microscopy we devised the it study to determine which methods would be appropriate for long term

prospective studies The results of this study suggest that in longitudinal studies a) more than six specular micrographs be taken during the first (baseline) examination in order to obtain quality photographs b) that the replicate measurement (Mode B) be utilized and c) the same observer be used to count the cells. Given that these normal subjects had no change in cell density over the period of study variations in cell density of ± 6% are within the limits of measurement. Since recounting the same proofs by a different technician may vary on the average by 4% the same technician should be used in follow up evaluations if possible

Acknowledgment

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Table III
Analysis of Variance of Endothelial Cell Density (cells mm²)

Mode	Average Cell Density		F	P
	Test	Retest		
A	2682 1	2890 2	5 59	<0 0
B	2730 3	2719 2	0 09	NS

Table IV
Precision of Cell Density Measurements (cells mm²)

Standard Deviation (% CV)*	Mode A	Mode B
Intra se sion	139 (5%)	173 (6%)
Intra session	135 (5%)	60 (2%)
Intra pair	167 (6%)	-

* The coefficient of variation CV = sd/x̄ where sd is the standard deviation and x̄ is the mean cell density = 2753 cells/mm²

References

A & Azen S P (19 9) Statistical Analysis A Computer Oriented Approach ?nd on Academic Press New York.

P S (19?8) Corneal transplantation today J Cl n. Exp Ophthal. 40 13 26

?rst C. D Loones L. H & Nygaard P (1977) The clinical specular m croscope Docum. hal. 44 57 5

e W M & Kaufman H E. (19?6) Specular microscopy of human corneal endothelium vo Amer J Ophthal. 81 319 3?3

W Sh p R C Stark W J & Maumenee A E. (19 7) Quantative corneal endothelial uation in intraocular lens mplantat on ?nd cataract surgery Amer J Ophthal. 84 80

A. Cable M K Hoffman C E & Hanna C (1978) Endothelial cell population changes uman cornea during l fe Arch Ophthal (Chicago) 96 ?031 2035

ell A E. (1971) Analyzing Qual tative Data Methuen London

ng S & Gundersen H J (19 8) The precis on of unbiased estimates of numerical s ty of endothel al cells in donor corneas Acta Ophthal (Kbh) 56 93 80?

Inc (19 ?) Publ cat on SC-1 Gainsville Florida.

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CORNEAL THICKNESS AND ENDOTHELIAL DAMAGE AFTER INTRACAPSULAR CATARACT EXTRACTION

BY

THOMAS OLSEN

In a prospective study corneal thickness and specular microscopic findings of corneal endothelium are reported in 37 patients undergoing intracapsular cataract extraction Central endothelial cell loss was estimated six months after the operation and was found to correlate significantly to the immediate post-operative increase in central corneal thickness A subgroup of patients showing slight endothelial dystrophy prior to the operation showed a significantly higher increase in corneal thickness fourth day after the operation. Six months after the operation a significant residual increase in corneal thickness was found for this group while the rest of the patients had returned to near pre-operative levels No correlation was found between cell loss and residual corneal thickness increase at this time Six months after the operation a vertical difference in cell density was found This difference could be correlated to the age of the patient presumably indicating a less complete redistribution of the cell population in older patients

Key words cataract extraction – cell loss – corneal thickness – endothelium specular microscopy

The damage exerted on the corneal endothelium during cataract extraction been the subject of several specular microscopic studies (Bourne & Kaufman Cheng et al 1977 Forstot et al 1977 Hirst et al 1977 Rao et al 19 8 D Waltman 1978 Rao et al 1979 Galin et al 1979 Abbott & Forster 19 working hypothesis has been that the amount of the endothelial trauma i.e. d loss is somehow related to the function of the endothelium and therefore to c hydration The information yielded by the endothelial reflex on this re however still unsettled

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post-operative endothelial cell density varies with time and location on the ... Evidence is now accumulating that the gradual decrease in cell density seen ...s after the operation (Hirst et al 1977 Rao et al 1978 Galin et al 1979) is ... l by a redistribution of the cell population (Rao et al 1978 Sugar 1979) ... g with time to even out imbalances in cell density created during surgery ... nplies that a lowered central cell density is an inaccurate index of total cell loss ... early phases after the operation

...s study reports the immediate effect of endothelial damage on corneal ... ness following intracapsular cataract extraction In order to improve estima... f the cell loss post-operative cell densities were not estimated until six months ... urgery

Subjects and Methods

...l of 45 subjects with senile cataract entered the study This group comprised all patients ...utively admitted to the eye department during a two months period where indication ...tracapsular cataract extraction was found Patients with co-existing eye diseases such as ...oma uveitis or corneal diseases were excluded Generally patients were not ad ocated ...ry if endothelial dystrophy was revealed in routine slit lamp examination Not seldomly ...ver the specular microscopic examination revealed a guttate endothelium in the ...thelial reflex which was not readily detected in ordinary slit lamp examination In such ... surgery was not abandoned and the patients were included in the study

...e operational procedure was intracapsular cryoextraction with corneal incision and ...lysis For irrigation a Ringer solution was used The wound was closed with running 10-0 ...n suture The operations were performed by a number of surgeons No regard was paid ...e particular surgeons experience Occurrence of vitreous loss or other pre-operative ...plications did not exclude the patient from the series

...ior to surgery the central endothelium of all patients were photographed with a contact specular microscope (Olsen 1979) The central corneal thickness was measured ... day before and on each of four days after surgery using a modified Haag Streit ...iometer (Ehlers & Sperling 1977) All measurements were single determinations taken as ...losest 5 μ position on the scale reading of the pachometer and were done by the author ...tly after noon The standard error of single determinations with the present method has ...utively been found to be 5-6 μ (about 1%) estimated from a large (>90) number of ...surements of several subjects

...x months after the operation the patients were asked to attend the clinic for reexamina... The central endothelium was photographed as described above and in addition an area ... mm superiorly to the center of the cornea was photographed by directing the gaze of ...tralateral eye Again corneal thickness was measured Intraocular pressure was measured ...n an applanation tonometer attached to the slit lamp Seven patients did not show up for ...reexamination One patient was excluded because of post-operative glaucoma Age range ...he remaining patients 16 men and 21 women was 57 87 years with a mean of 73 6 years ...ese 37 patients are reported on in the following Unless specified otherwise statistical ...lyses were based on distributional methods For comparison of means Student s *t* test was ...ployed

Results

Pre operative and post operative central cell density of opera ed eye was (± SD) 2541 (± 423) and 1894 (± 501) cells/mm² respectively with a mean of *25 1 (± 16 4) % Pre-operative central corneal thickness of operated eye* (± 0 031) mm No correlation was found to pre-operative cell density (r 0 3) The immediate increase in central corneal thickness was 0 08 (± 0 0 (± 0 050) 0 059 (± 0 027) and 0 054 (± 0 028) mm the first, second, third fourth day after the operation respectively For each day this increase was f correlate significantly to the central cell loss (r = 0 73 0 59 0 56 and 0 0 001 for day one through day four respectively) The strongest correlation thus found on the first post-operative day (Fig 1) Dotted line in Fig 1 ind regression line y on x calculated using the method of least squares for the increases below 250 μ Intersection on ordinate is not significantly differen the origin

Six of the patients turned out to have guttae in the endothelium as reveal the pre operative photographs of the central endothelium These change

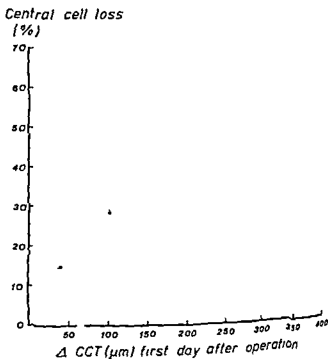


Fig 1

Correlation between first day post-operative increase in central corneal thickness (C central endothelial cell loss estimated six months after cataract extraction Do indicates regression line y on x (r = 0 73 $P < 0\,001$)

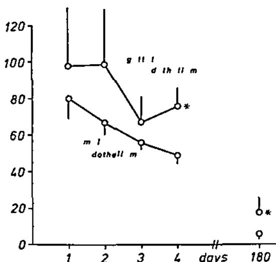


Fig 2

n post-operative increase in central corneal thickness (CCT) in 31 patients with normal othelium and 6 patients with minor dystrophic changes in the endothelium Asterisks ate significant ($P < 0.05$ by Student's t test) difference among the groups on day four persistent elevated thickness six months after surgery for the group with guttate endothelium Vertical bars indicate standard errors of the mean

teral Mean pre-operative corneal thickness of this group was 0 540 (± 0 017) not significantly different from the rest of the patients The post-operative rease in corneal thickness for this group was larger than in the patients with mal endothelial reflex and became significantly different fourth day after the ration (Fig 2) The mean cell loss of 29 7 (± 20 1) % for this group was however t significantly different from the rest of the patients

or the total group neither pre-operative cell density visible pleomorphology of cells pre-operative corneal thickness age nor sex was significantly related to the ckness increase or central cell loss

Six months after the operation central corneal thickness was almost normalized in e normal group Mean residual thickness increase was 0 006 (± 0 018) mm not nificantly different from zero In the group of pre-operative indothelial guttae e residual thickness increase was 0 018 (± 0 020) mm which is close to but gnificantly ($P < 0.05$) different from zero In these patients the endothelial anges had worsened in all cases that is the defects in the endothelial reflex were rger and more numerous than before the operation (Fig 3) No guttai like anges were found in those eyes with previous normal endothelial reflex (Fig 4)

No correlation was found between cell loss and residual corneal thickness a time in the entire group (r = 0 22 $P > 0\ 1$) All corneas were clear Cr thickness of unoperated eye showed a mean change of −0 001 (± 0 ... −0 003 (± 0 012) mm in the normal and guttae group respectively

The superior counts found six months after the operation were as a group ... that the central counts Mean decrease from central to superior counts was ... range −3 to +57% This vertical difference in cell density was found to co... significantly to the age of the patient (Fig 5) For graphic simplicity the data ... been pooled and averaged in three age groups No difference was found be... the vertical density difference in the guttae group as compared to the ... group (mean values 26 5 (± 18 5) % n = 3 vs 18 0 (± 16 4) % n = 29 respe... $P < 0\ 4$) In five patients counts from the superior region were not available ... poor quality of photographs or extensive guttae-changes No relation was f... between the vertical density difference and residual corneal thickness ... months after surgery

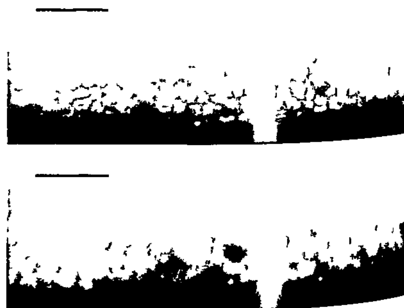


Fig 3

Central corneal endothelium before (top) and six months after (bottom) ... cataract extraction in a seventy-one year-old woman with guttate endothelium T... density has decreased 49% from 2480 to 1270 cells mm² Central corneal thickness ... 0 190 mm first day after the operation Bar = 100μ

Fig 4

ntral corneal endothelium before (top) and six months after (bottom) intracapsular aract extraction in a sixty nine year-old woman The cell density has decreased 3-% from 0 to 1820 cells mm² Central corneal thickness increased 0 190 mm first day after the operation Bar 100μ.

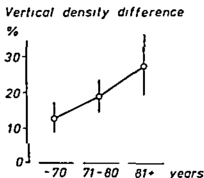


Fig 5

lean difference in cell counts from the central endothelium and ? 3 mm superiorly found six onths after intracapsular extraction The ertical density difference is sign ficantly corre ated to the age of the patient. (Sperman s rank correlat on coefficient r 0 39 $P < 0\ 05$) Bars indicate standard errors of the mean

Discussion

The mean cell loss reported after intracapsular cataract extraction ranges [illegible] 21% (Bourne & Kaufman 1976 Cheng et al 1977 Forstot et al 19[illegible] [illegible] 1977 Rao et al 1978 Drews & Waltman 1978 Galin et al 1979 Abbott & [illegible] 1979) In these studies the post-operative time until evaluation generally [illegible] from a few days to several months The mean cell loss of [illegible]% found six [illegible] after the operation in the present study may seem higher than in the studies [illegible] above Some of this discrepancy undoubtly is accounted for by the l[illegible] post-operative period in the present study Because of the sliding phenom[illegible] central counts may be expected to indicate total cell loss better the l[illegible] post operative follow up period Galin et al (1979) state that the post-oper[illegible] decrease in central counts is minimal after three months The still present [illegible] density difference found in the present study after six months (Fig 5) indicate[illegible] a complete redistribution of the cell population has not taken place at this [illegible] least in the age range studied Whether the central count after this time [illegible] reflects the mean decrease in cell density is unclear To answer this a [illegible] mapping of the corneal endothelium post operatively seems necessary

Another factor which must be considered when comparing cell losses report[illegible] different investigators is that only clear corneas can be studied At the [illegible] follow up examination all corneas were clear ensuring that no endothelial [illegible] was excluded on the grounds of an oedematous cornea a problem which ma[illegible] in the early post operative days and especiallly in case of great cell loss

The average increase in corneal thickness found in the present study in the [illegible] post operative days seems to be in agreement with the results of Norn (1973) [illegible] & Maumenee (1975) and Bramsen et al (1978) Somewhat greater th[illegible] increase was found by Cheng et al (1977) Giardini & Cambiaggi (1956) in a [illegible] of extra and intra capsular extractions found an average of 45% increa[illegible] corneal thickness on third day after the operation Presumably this high in[illegible] may be due to the different surgical technique employed twenty years ago [illegible] 1973)

Most authors agree that the corneal thickness returns to normal less th[illegible] months after the operation (Cheng et al 1977 Norn 1973 Wood & Mau[illegible] 1975) even in the case of very high immediate encrease (Giardini & Camb[illegible] 1956) At variance is the finding of Miller & Dohlman (1970) who stated th[illegible] of 50 unilateral aphakic subjects more than six months after the operation showed increased corneal thickness on the operated side As was shown by W[illegible] Maumenee (1975) and as was the tendency in the present investigation ultimate thickness depends on the pre-operative condition of the endothel[illegible]

iation was given on the status of the endothelium in the series reported by & Dohlman (1970)

present investigation revealed a strong correlation between the immediate l thickness and the cell loss index i e the central cell loss Like the situation estimates of the cell loss central corneal thickness increase can only be ded as an index of the total volumen change or water intake of the cornea. ner the central increase represents the mean thickness is dependent on the distribution within the cornea, which varies considerably with time and among ent individuals (Giardini & Cambiaggi 1956) Generally however the cornea ker in the upper part and thinner in the lower part with an intermediate ness in the center By expressing the cell loss as per cent of initial value the onship depicted in Fig 1 is in fact a correlation between an index of the water e of the cornea and an index of the area broken down of the endothelium as a t of the surgery This relationship bears a remarkable resemblance to the ion in acute glaucoma (Olsen 1980)

e reason why other authors who have measured both the corneal thickness the central cell loss did not find this close relationship may be found in the ter post-operative period studied Bourne & Kaufman (1976) noted however those corneas with significant cell loss also had greater increase in thickness ng et al (1977) noted that cataract extraction with lens implantation gave more loss and greater increase in corneal thickness than without lens implantation erimentally the quantitative correlation between damaged endothelial area and eal thickness response has been demonstrated by Honegger (1962) and Van n et al (1977)

is noteworthy that the cell loss observed in the present study did not induce a manent decrease in the deturgescence function of the cornea Only those with operative guttate endothelium had not returned to pre-operative corneal kness after six months It appears that the integrity of the normal endothelium outh depr—ed up to 63% of its cells (found in the present study) alone can ntain normal corneal thickness at least in the range of lowered cell densities erved in the present study A similar observation has been made by Forstot et al 77) and in corneal grafts (Bourne & Kaufman 1976a Laing et al 1976 Sato et 1978) Another remarkable result was that no newly formed guttae had eloped as a result of the cell loss This challenges the hypothesis held by Capella 79) that the cell damage as such initiates the production of abnormal Descemet s embrane material and add some evidence against the view of Fuchs endothelial strophy being a low cell density syndrome (Olsen 1980)

It was surprising to find a persistent vertical difference in cell density six months ter surgery Whether this imbalance in cell density was a stable situation or a rther reduction would occur with time is yet unclear Apparantly the mobility of

the cells is dependent on the age of the patient as shown in Fig 5 The fu... significance of these findings remains unknown It is hardly doubtful how... if the cells were not able to move there was no way by which the endothel... reestablish an intact barrier function in response to injury

Acknowledgments

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References

Abbott R L & Forster R K (1979) Clinical specular microscopy and ... *Arch Ophthal (Chicago) 97* 1476 1479

Bramsen T Corydon L & Ehlers N (1978) A double blind study of the effect of tranexamic acid on the central corneal thickness after cataract extraction. Acta ... *(Kbh) 56* 121 126

Bourne W M & Kaufman H E (1976) Cataract extraction and the corneal endoth... *Amer J Ophthal 82* 44 47

Bourne W M & Kaufman H E (1976a) The endothelium of clear corneal transplants ... *Ophthal (Chicago) 94* 1730 1732

Capella J A (1972) Regeneration of endothelium in diseased and injured corneas ... *Ophthal 74* 810 817

Cheng H Sturrock G D Rubenstein B & Bulpitt C J (1977) Endothelial cell ... corneal thickness after intracapsular extraction and lens implantation ... controlled trial (interim report) *Brit J Ophthal 61* 785 790

Drews R C & Waltman S R (1978) Endothelial cell loss in intraocular lens placement ... *Int ocular Implant Soc 4* 14 16

Ehlers N & Sperling S (1977) A technical improvement of the Haag Streit pachometer ... *ophthal (Kbh) 55* 333 336

Forstot S L Blackwell W L Jaffe N S & Kaufman H E (197) The effect of ... lens implantation on the corneal endothelium *Trans amer Acad Ophthal* ... 195 203

Galin M A Lin L L Fetherolf E Obstbaum S A & Sugar A (1979) Time ... corneal endothelial cell density after cataract extraction *Amer J Ophthal* ...

Giardini A & Cambiaggi A (1956) Recherches sur l'epaisseur corneenne apres extra... la cataracte *Ophthalmologica 134* 41 50

Hirst L W Sinp R C Stark W J & Maumenee E (1977) Quantitative corneal ... evaluation in intraocular lens implantation and cataract surgery *Amer J Ophthal* ... 775 780

Honegger H (196) Quantitative Untersuchungen Uber die Hornhautendothel... ration in vivo *v Graefe Arch Ophthal 165* 31 4

Laing R A Sandstrom M Berrospi A R & Leibowitz H M (1976) Morphological ... in corneal endothelial cells after keratoplasty *Amer J Ophthal 82* 459 464

) & Dohlman C. H (1970) Effect of cataract surgery on the cornea *Trans amer Acad* *-ial Otolaryng 74* 369–374
f S (1973) Pachometric study on the influence of corneal endothelial vital staining *phthal. (Kbh) 51* 679–686
T (1979) Non-contact specular microscopy of human corneal endothelium *Acta* *al (Kbh) 57* 986–998
T (1980) On the significance of a low endothelial cell density in Fuchs endothelial ophy A specular microscopic study *Acta ophthal (Kbh) 58* 111–116
T (1980) The endothelial cell damage in acute glaucoma On the corneal thickness onse to intraocular pressure *Acta ophthal. (Kbh) 58* 257–266
N Shaw E L Arthur E & Aquavella J (1978) Morphological appearance of the ng corneal endothelium *Arch Ophthal. (Chicago) 96* 2027–2030
N Shaw E L Arthur E & Aquavella J (1979) Endothelial cell morphology and eal deturgescence *Ann Ophthal 11* 885–899
Ota Y., Kimura C Tanishima T & Mishima S (19 8) The endothelium of the eal graft morphological and functional aspects *Docum Ophthal Proc Series 20* 73–81
A (1979) Clinical specular microscopy *Surv Ophthal 24* 91–32
orn D L Sendele D D Seideman S & Buco P J (1977) Regenerative capacity of the eal endothelium in rabbit and cat *Invest Ophthal Vis Sci. 16* 597–613
. W J & Maumenee A E (1975) Corneal thickness after cataract surgery *Trans amer* *I Ophthal Otolaryng 79* 631–634

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References

Abbott R L & Forster R K (1979) Clinical specular microscopy and intraocular *Arch Ophthal (Chicago) 97* 1476–1479

Bramsen T Corydon L & Ehlers N (1978) A doubleblind study of the effect of tranexamic acid on the central corneal thickness after cataract extraction *Acta (Kbh) 56* 121–126

Bourne W M & Kaufman H E (1976) Cataract extraction and the corneal endothelium *Amer J Ophthal 82* 44–47

Bourne W M & Kaufman H E (1976a) The endothelium of clear corneal transplants *Ophthal (Chicago) 94* 1730–1732

Capella J A (1972) Regeneration of endothelium in diseased and injured corneas *Ophthal 74* 810–817

Cheng H Sturrock G D Rubenstein B & Bulpitt C J (1977) Endothelial cell corneal thickness after intracapsular extraction and lens implantation a controlled trial (interim report) *Brit J Ophthal 61* 785–790

Drews R C & Waltman S R (1978) Endothelial cell loss in intraocular lens placement *Intraocular Implant Soc 4* 14–16

Ehlers N & Sperling S (1977) A technical improvement of the Haag Streit pachometer *ophthal (Kbh) 55* 333–336

Forstot S L Blackwell W L Jaffe N S & Kaufman H E (1977) The effect of lens implantation on the corneal endothelium *Trans amer Acad Ophthal Otol* 195–203

Galin M A Lin L L Fetherolf E Obstbaum S A & Sugar A (1979) Time analysis of corneal endothelial cell density after cataract extraction *Amer J Ophthal 88* 93

Giardini A & Cambiaggi A (1956) Recherches sur l epaisseur corneenne apres extraction de la cataracte *Ophthalmologica 134* 41–50

Hirst L W Snip R C Stark W J & Maumenee E (1977) Quantitative corneal endothelial evaluation in intraocular lens implantation and cataract surgery *Amer J Ophthal* 775–780

Honegger H (1969) Quantitative Untersuchungen Über die Hornhautendothelregeneration in vivo *von Graefes Arch Ophthal 165* 31–42

Laing R A Sandstrom M Berrospi A R & Leibowitz H M (1976) Morphological changes in corneal endothelial cells after keratoplasty *Amer J Ophthal 82* 459–464

arent adhesive tape which could be removed temporarily during measure

gas in each tank was analysed by a specialised laboratory and claimed to be te within 0 1% Two oxygen mixtures were used 2 1% oxygen and 3 15% n corresponding to 16 and 24 mmHg

view of the results of Polse & Mandell (1970) who found no significant nce between dry or humidified gas on corneal hydration we used only dry ectly from the storage cylinders

al sensitivity measurements

l sensitivity was measured using the Cochet Bonnet (1960) aesthesiometer based on trument devised by Boberg Ans (1955) The instrument consists of a nylon monofila of 0 12 mm diameter that can produce pressures ranging from 11 to 200 mg/0 0113 The aesthesiometer was mounted in a holder so that it could be moved in the x y and z by means of three knobs Thus it was possible to achieve reliability in stimulation of ne corneal point a steady speed of application and a perpendicular corneal contact A l point near the lower limbus was stimulated and the slightest bend of the nylon wire fined as corneal contact

ing measurements the subjects fixated a target directly in front and considerably above normal line of sight A peripheral corneal point was chosen so as to reduce apprehension (Bonnet & Millodot 1965)

surements of corneal touch threshold (CTT) were made subjectively (Millodot 1973) xperiment began with the lowest pressure and continued in an ascending fashion At

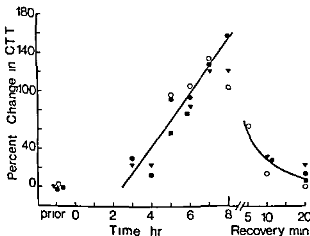


Fig 1

eal Touch Threshold as a function of time with exposure to 2 1% oxygen and recovery ● ○ subject A ▼ subject B ■ subject C

each predetermined length of the monofilament (with increments equal to 0.5 cm ... contacts were made with at least one blank to test the subjects reliability The ... indicated when he or she felt the probe by operating a buzzer From these ... CTT was defined as the length of the monofilament at which the subject responded ... of the number of stimulations This length was converted into pressure using the calibrated curve for the instrument All measurements were taken when the humidity ... room ranged between 50% and 60% because the nylon monofilament is affected by ... The accuracy of this measurement is usually within ± 5%

Procedure

Both eyes of the subject were tested for corneal sensitivity in the morning ... experiment The subject had been awake for at least two h in order to ... diurnal effect (Mandell & Fatt 1965 Hirji & Larke 1978 Millodot 19... air tight goggles (with the adhesive tape) were fitted firmly to the subject ... the gas was then turned on Measurements of corneal sensitivity were made ... after three h by removing the transparent adhesive tape and increasing the flow of gas The procedure took between 40 and 55 seconds and the adhesive was immediately stuck back on the goggle Following the experimental session ... were again collected for up to 40 min to assess recovery All data were ... three subjects because of the constraints produced by keeping the subjects ... to a gas tank through the goggles for so many h All measurements were ... entirely on one subject a week later

Results

Fig 1 shows the increase in CTT with 2 1% O_2 for the three subjects and ... session on one of them as compared to the value obtained prior to the ... experiment After about three h CTT rises rapidly and linearly reach... 130% increase at the end of the experiment (8h) Recovery is quite fast ... deal of corneal sensitivity had returned within 20 min The results are ... with 3 15% O_2 as illustrated in Fig 2 However it takes longer (about 4 ... CTT begins to rise Afterwards the increase is very rapid reaching some ... the end of the experiment (10 h) With both oxygen mixtures there is ... providing further proof that sensitivity had indeed diminished during the experiment

The latency of several h before any appreciable loss of corneal sensitivity explains why Polse (1978) did not find any change in sensitivity in his ... since he carried out his measurements for a period of only 2 5 h

Measurements on the control eye showed no appreciable difference d... experimental session indicating that the goggles had no effect, as such ... cornea

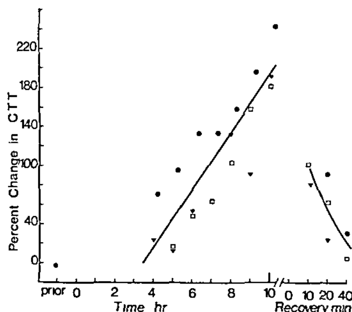


Fig 2

al Touch Threshold as a function of time with exposure to 3 15% oxygen and recovery ● o subject A ▼ subject B

Comment

esults of this investigation show that exposing the cornea to a partial pressure igen of 2 1% (or 16 mmHg) and 3 15% (24 mmHg) lead to a progressive and ed increase in corneal touch threshold

h a partial oxygen pressure of 16 mmHg it took nearly 6 h to observe an ise in CTT (or loss of sensitivity) of 100% Whereas it took some 7 h with a ure of 24 mmHg (see Fig 3) In another study by Millodot & O Leary (1979) it ound that when the eyes are closed that is the oxygen pressure at the corneal ce is 55 mmHg an equal increase in CTT occurs after 15 h This result is also d in Fig 3 And with the wear of hard contact lenses (PMMA) Millodot (1976) lished that after 10 h CTT was increased by 100% According to Farris et al.) the oxygen deprivation induced by wearing hard contact lenses is greater that caused by lid closure and from the data of Fatt & Hill (1970) it can be ated after taking into account the effect of blinking to average around 38 Ig Inserting this value in Fig 3 shows that there is a clear relationship between

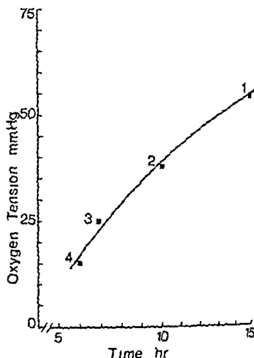


Fig 3

Oxygen tension at the corneal surface and time to produce a 100% loss in corneal sensitivity 1 eyelid closure (Millodot and O Leary 1979) 2 hard contact lenses (Millodot 1978) 3 15% oxygen mixture 4 2 1% oxygen mixture

the loss of corneal sensitivity and the partial oxygen pressure at the corneal surface. Thus it appears unequivocal that corneal sensitivity diminishes markedly when oxygen tension at the corneal surface is below normal This conclusion is consistent with the fact that after permanent wear of contact lenses with high oxygen transmission corneal sensitivity is reduced by 100% after 16 weeks (Larke & 1979)

Since these alterations occur at oxygen tensions well above that at which the cornea starts swelling (Polse & Mandell 1970) it would be inappropriate to assume that corneal thickness measurements are satisfactory indicators of a normal cornea. At present it seems that corneal touch threshold measurements give a better indication of disturbed corneal physiology and it is suggested that this function be worth monitoring clinically

References

Ans J (1955) Experience in clinical examination of corneal sensitivity *Brit J Ophthal* 5–726

R & Millodot M (1965) L esthesie Corneenne Sa mesure dans l obscurite *Clin* 6 74–78

& Bonnet R (1960) L esthesie Corneenne *Clin Ophthal 4* 9–27

L Takahashi G H & Donn A (1967) Corneal oxygen flux in contact lens wearers rard L J (ed) Corneal and scleral contact lenses *Proc Int Cong* pp 413–425 C V Co St Louis

& Hill R M (1970) Oxygen tension under a contact lens during blinking – a rison of theory and experimental observation *Amer J Optom 47* 50–55

E & Nordquist L (1955) The hydration of the cornea I The transport of water he cornea *Amer J Opthal 40* 100–111

K & Larke J R (1978) Thickness of human cornea measured by topographic metry *Amer J Optom 55* 97–100

R & Hirji N K (1979) Some clinically observed phenomena in extended contact lens *Brit J Opthal 63* 475–477

R B & Fatt I (1965) Thinning in the human cornea on awakening *Nature 208* 293

M (1972) Diurnal variation of corneal sensitivity *Brit J Ophthal 56* 844–847

M (1973) Objective measurement of corneal sensitivity *Acta Ophthal (Kbh) 51* 334

M (1976) Effect of the length of wear of contact lenses on corneal sensitivity *Acta al (Kbh) 54* 721–730

M & O Leary D J (1979) Loss of corneal sensitivity with lid closure in humans *J x s 29* 417–491

A (1978) Etiology of corneal sensitivity changes accompanying contact lens *Ophthal 17* 1202–1206

A & Mandell R B (1970) Critical oxygen tension at the corneal surface *al (Chicago) 84* 505–508

G K & Ozanics V (1952) Importance of atmospheric oxygen for maintena l properties of the human cornea *Science 115* 140

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THE FATE OF PRESERVED AND TRANSPLANTED HUMAN CORNEAL ENDOTHELIUM

BY

PEKKA RUUSUVAARA

This paper evaluates the numbers of corneal endothelial cells that [illegible] transplantation The donor endothelium was photographed with a spec[illegible] microscope both before enucleation and in situ after keratoplasty The cell density was measured in 16 corneas from donors with choroidal melanoma Of these donor corneas 12 were cryopreserved two were preserved in McCarey and Kaufman s (M K) medium and two were transplanted fresh The [illegible] follow up period after keratoplasty was 11 months

The mean endothelial cell loss for the whole series was found to be [illegible] The mean cell loss for the cryopreserved corneas was 55% In the four [illegible] recipients with donor corneas that had been stored in M K [illegible] transplanted fresh the mean cell loss was 32%

The corneas preserved in M K medium had the highest cell density in the transplants with cell losses of 21 and 22% Cell losses in the two corneas transplanted fresh were 40 and 44% Cell losses in the cryopreserved grafts had a wide variation 33 77% No correlation could be found between cell [illegible] and either the age of the donor or the duration of preservation

Freezing and thawing was found to damage a proportion of the cells [illegible] they did not stain with para nitro-blue tetrazolium (p-NBT) after [illegible] Transmission and scanning electron microscopy also revealed changes in the intercellular spaces and some cell disruption in cryopreserved grafts

Key words corneal graft endothelium – endothelial ultrastructure – corneal preservation – specular microscopy – cell viability – cryobiology

Clinically good results have been reported in penetrating keratoplasties with corneas preserved by several different methods Measurements of graft endothelial cell densities postoperatively with the specular microscope have established viability of donor endothelial cells after preservation of whole eyes [illegible]

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ber and of excised corneas in M K medium and by freezing (Bourne & nan 1976b Ruusuvaara 1979)
ording to earlier reports (Bourne & Kaufman 1976a Laing et al 1976b et al 1978) endothelial cell density decreases with age (cell size increasing ortionally) The difference in cell density between the right and left eye of the patients is so small that study of the cell population of one eye gives a result enough to represent the cell population of the fellow eye although there is variation in cell density between different individuals Previously it has not possible to calculate exactly how many cells/mm² are lost in each keratoplasty use there was no way of knowing the exact preoperative cell density of the r in vivo With the advent of the specular microscope (Maurice 1968) the tion has completely changed
ie purpose of this study was to evaluate the exact numbers of cells lost during procedures of cryopreservation or storage in M K medium and during ipulation of the corneal button in transplantation The corneas were examined a contact specular microscope Because of the difficulty of photographing the eal endothelium of enucleated eyes I photographed the endothelia first in the of the donors with choroidal melanoma before enucleation and later in situ in recipients after keratoplasty This procedure permits direct determination of proportion of endothelial cells that have survived transplantation
sing the corneoscleral rim left after removal of the corneal button (Ruusuvaara 9) after cryopreservation and storage in M K medium I also compared the amicroscopic changes found with the results of vital staining of the endothelia with the cell density in specular microscopy

Material and Methods

ors and recipients

donors were 16 patients with malignant choroidal melanoma In nine cases the e endothelium was photographed in vivo before enucleation of the eye and in after keratoplasty In seven cases the endothelium of the donor s fellow eye photographed within a few months after enucleation of the melanomatous eye comparison with that of the graft
he exact endothelial cell loss during preservation and manipulation in kera lasty was calculated from the difference in endothelial cell density between the ior cornea before enucleation (or the donor s healthy fellow eye) and the graft r keratoplasty
he recipients ranged in age from 17 to 64 years and the donors from 27 to 72 rs The proportion of men to women among the recipients was 11 to 5

Ten patients had keratoconus one had phlyctenular keratitis and two [illegible] matous keratitis One had an alkali burn of the cornea and two had corneal [illegible] of unknown origin In five cases the corneal beds of the recipients were [illegible] zed Only one patient was aphakic before keratoplasty Eleven of the 16 [illegible] received grafts with 0 1 HLA mismatches and only five had 2 HLA mismatches [illegible] the role of histocompatibility in this series seems to be quite small All the grafts were cryopreserved and used for keratoconus patients The average [illegible] up period was 11 months with a deviation of ± 9 months

Type of preservation of the donor cornea

In 12 cases the corneas were cryopreserved (Capella et al 1965) with a [illegible] The cryopreservation time varied from 1 day to 3 years with an average [illegible] months Two corneas were transplanted after preservation in M K [illegible] (McCarey & Kaufman 1974) for 1 and 3 days Two corneas were transplanted fresh The cadaver time for all these corneas was minimal because all [illegible] enucleated from living patients

Donor button excision and operative technique

Those corneas that were to be cryopreserved or preserved in M K medium were [illegible] with a large scleral rim and excision from the globe was completed with scissors [illegible] 1975) After thawing the graft was punched from the endothelial side as reported [illegible] earlier paper (Ruusuvaara 1979) In two cases the graft was excised directly from the epithelial side of the cornea with the trephine in such a way that only a 7 mm graft [illegible] for immediate transplantation

All keratoplasties were performed by two surgeons (SV KK) The operative technique [illegible] the same and 10-0 monofilament as continuous or single sutures was used

Micrography of the endothelium

The endothelia in the centres of the donor corneas and of the grafts were photographed through a modified clinical specular microscope (Bourne & Kaufman 1976) [illegible] photograph (magnified x 500) the area counted was a rectangle of 0 01 mm² and [illegible] wholly inside this rectangle and those cut by two adjacent sides were counted Each [illegible] was counted in the four possible different ways and the average was taken as the [illegible] To obtain a reliable result 3 5 different fields of view were counted

Vital staining

After removal of the corneal button each corneoscleral rim which had been cryopreserved [illegible] stored in M K medium was stained histochemically Staining was done with para-nitro [illegible] tetrazolium (p-NBT) which causes precipitation of the dye in the cytoplasm [illegible] endothelial cell if the enzymes are still functioning (Robbins et al 1960) The [illegible] corneal endothelium was then examined for viable (stained) cells and non-viable [illegible] cells The rims of the corneas stored in M K medium were frozen with liquid [illegible] thawed before staining and the cryopreserved material was stained after thawing

·on microscopy of donor endothelium

-eripheral donor endothelium was analysed in every case of cryopreservation or storage (medium. For ultrastructural analyses a piece of the peripheral corneal rim was fixed glutaraldehyde with 0 1 M phosphate buffer pH 7.3 The tissue was post fixed with mium tetroxide in phosphate buffer The specimen were dehydrated in alcohol and lene oxide embedded in Epon resin and sectioned with a Reichert ultramicrotome ns were post stained with lead citrate and uranyl acetate Cell morphology and the ity of the cell structure were analysed at the Department of Electron Microscopy iki University with the JEM 100 S electron microscope

ning electron microscopy of donor endothelium

mens for scanning electron microscopy (SEM) were prepared from 5 cryopreserved ras and 2 corneas stored in M K medium Pieces of the peripheral corneal rim were fixed glutaraldehyde with 0 1 M phosphate buffer pH 7.3 post fixed in phosphate-buffered smium tetroxide dehydrated in a graded series of water-ethanol and critical point dried CO_2 The dried tissues were then fixed to specimen stubs with conductive silver paint coated with carbon and gold in a Blazer BA 3 evaporator Specimens were examined in a JSM L3 scanning electron microscope at 20 kV

Results

mean cell loss in each preservation group is shown in Table I The mean othelial cell loss for the 16 corneas was 49% The mean cell loss for the 12 preserved corneas was 55% In the four other patients in whom the donor iea had been stored in M K medium or transplanted fresh the mean cell loss 32% The two fresh corneas had a mean cell loss of 42% For the two corneas ed in M K medium the mean cell loss was 22% For all preservation groups the n post-operative period was 11 12 months The mean donor age was highest years) for the cryopreserved material.

able II shows the different parameters for each individual case donor age pient age type and time of preservation post-operative period donor and graft othelial cell density and the percentage cell loss in each case

1 the cryopreserved corneas from melanomatous eyes cell loss during preserva and keratoplasty varied from 33% to 77% (Fig 1A B) No correlation existed veen length of preservation and endothelial cell loss in case 1 for example with longest cryopreservation time 3 years cell loss was only 33% The two highest losses were in cases 11 and 12 The latter patient had a vascularized lime burnt nea which is known to be one of the most difficult cases with a poor prognosis e former with keratoconus had a complicated post-operative bacterial infection n the two freshly transplanted corneas used as controls for the effects of servation and storage cell losses were 40 and 44% The transplanted endothelial

Table I

Endothelial cell densities (± SD) of donor corneas and grafts

Method of preservation	Number of donor eyes	Mean endothelial cell density of donor corneas (cells/mm²)	Mean endothelial cell density of transplants (cells/mm²)	Mean cell loss (cells/mm²)	Cell loss (%)	Mean postop period (months)	Mean age of donors (years)	Mean age of recipients (years)
Cryopreservation	12	2533±308	1149±440	1384±386	55	11	55	34
Others	4	2860±212	1944±211	925±393	32	12	45	46
(M K medium)	(2)	(2700±111)	(2113± 88)	(568± 53)	(22)	(12)	(45)	(38)
(fresh)	(2)	(3037± 35)	(177 ±106)	(1262± 71)	(42)	(12)	(44)	(4)
Total	16	2617±318	1317±5[illegible]	1[illegible]1±427	49	11	53	37

Table II

Eur No	Method of preservation	Length of preservation	Donor age (years)	Donor mean endothelial cell count (cells/mm²)	Mean graft endothelial cell count (cells/mm²)	Cell loss %	Lost operative period (months)	Recipient age (years)	Recipient Diagnosis	Vasc
1	cryo	3 y	72	2208	1425	33	2	23	Conus	–
2	–	7 mo	27	3200	2100	34	15	24	Conus	–
3	–	4 mo	37	2637	1750	34	[illegible]	17	Conus	–
4	–	7 mo	59	2100	1925	19	6	50	Conus	–
5	–	8 mo	72	2163	1900	1	14	37	Conus	–
6	–	6 mo	69	1975	883	55	[illegible]	27	Conus	–
7	–	8 d	51	2512	1100	56	36	61	Maculae c	+
8	–	1 5 mo	[illegible]	2158	1017	59	9	35	Conus	–
9	–	1 mo	47	28 0	1150	60	9	31	Parench k	+
10	–	3 y	66	2716	858	68	2	22	Conus	–
11	–	1 d	37	2125	600	75	12	16	Conus	–
12	–	6 d	64	[illegible]	600	77	9	21	Corrosion	+
13	M K	3 d	31	2600	2050	21	10	32	Conus	–
14	M K	1 d	59	2800	217	22	13	13	Parench k	+
15	Fresh	–	37	3062	1850	10	12	18	Maculae c	–
16	Fresh	–	51	3012	1700	14	11	60	Phlyct k	+

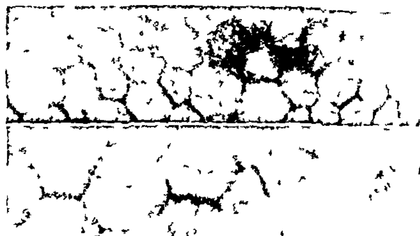


Fig 1 A B

A Central corneal endothelium of the donor before enucleation of the [illegible] The same endothelium photographed from the graft transplanted after [illegible] 1,5 months The cell densities are 2458/mm² in A and 1017/mm² in B (x [illegible]) [illegible]



Fig 2 A B

A Central corneal endothelium on specular microscopy of a melanomatous donor [illegible] The same endothelium photographed from the graft transplanted after storage for [illegible] M K medium Follow up period 10 months The cell densities are [illegible] in A [illegible] 2050 mm² in B (x 450) Bar = 50μ

ta ned the h ghest dens ties in the two corneas stored in M K med um with vation times of 1 and 3 days In these cases cell loss was only 21 and 22% (Fig

s after sta n ng

ng of the peripheral endothel um of corneas stored in M K med um revealed nal hexagonal cell pattern Different fields of view showed that all the cells venly stained and that in each cell the intensity of the dye was uniform Thus



F g 3 A B C

ansm s on electron m crograph of human corneal endo hel um preserved n M K um for 3 days Membranes of cells and nucleus (N) appear undamaged but some es (V) and perinuclear swell ng (as erix) are seen The la eral cell borders are normally lu ed and clo ely appo ed (arrows) T ght junct on (TJ) s ntact (x 6 000) B H gher f a on of the same endothel um show ng closely apposed con olu ed cell borders s) and t ght junct on (TJ) of adjacent cells (x 13 500) C Human corneal endothel um ved n M K med um and stained af er preservation for reduced n cot nam de aden ne leoude d aphorase Un form precip ta on of the dye ns de normal look ng endo hel al cells

A



B



Fig 4 A B C

A Transmission electron micrograph of cryopreserved human corneal endothelium intercellular spaces (IS) are highly enlarged and the cell membranes of adjacent separated from each other (arrows) Aslo some mitochondrial swelling and vacuoles cytoplasm are to be seen Cell membranes (arrows) and the nucleus (N) are intact membrane (DM) is seen in the lower position (x 3 500) B Higher magnification intercellular space (IS) seen in Fig A Cell membranes are attached to each other junction (TJ) macula adhaerens (arrow) and near the Descemet's membrane (double (x 12 000) C Cryopreserved human corneal endothelium stained for reduced adenine dinucleotide diaphorase Groups of unstained (damaged) cells are present normally stained cells

in the two corneas stored in M K medium the viability of the endothelium evaluated by nitro blue tetrazolium staining was 100% (Fig 3C) There was difference in viability between endothelia stored for 1 and 3 days

Similar staining was done on the peripheral rim of the cryopreserved (N = 12) after thawing and punching of the central graft. In these corneas cryopreserved endothelial cells showed morphological variability Furthermore intensity of the stain inside the cell cytoplasm varied and some cells vacuoles Those corneas (N = 3) in which mechanical trauma was suspected eliminated from the analysis The percentage of non stained cells in the cryopreserved corneas was sometimes as high as 15% when counts were made on an area 5 different fields of view (Fig 4 C) corresponding an area of 0 2 mm² in

Results of electron microscopy

ıg electron mıcroscopy

ıealed an ıntact endothelıum ın the penpher) of the cornea ın both cases ın he corneas had been stored ın M K medıum There was no pleomorphısm cell borders were well seen (Fıg 5 A) The nucleı of the preserved cells were ıble No dıstınct dıfference could be seen between the two corneas stored K medıum one for 1 day and the other for 3 days Only an occasıonal ted or lysed endothelıal cell was found among the normal lookıng hexagonal n both cases ıt was observed that the endothelıal cells formed a contınuous ıg on Descemet s membrane and had maıntaıned theır ultrastructural ty

ıe 5 cryopreserved corneal endothelıa studıed most samples showed clearly cell borders Moreover the polygonal cells had promınent nucleı There ırge areas where the endothelıal cells were normal lookıng and apparently but also patches where they were dısrupted Where dısrupted and lysed cells een they were commonly grouped ın rows or clusters of 5 10 cells In these ted cells the nucleus and cellular organelles were exposed No correlatıon was between the number of dısrupted cells seen ın SEM and the tıme of eservatıon (Fıg 5 B)

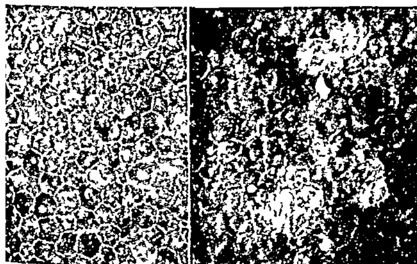


Fig 5 A B

nnıng electron mıcrograph of human endothelıum preserved ın M K medıum for 2 Normal mosaıc lıke polygonal endothelıal cells wıth ıntact cell membranes and nucleı) B Cryopreserved (8 months) human corneal endothelıum In thıs area some groups of cells are dısrupted and swollen among normal lookıng hexagonal cells (x 350)

Transmission electron microscopy

The peripheral endothelium of the corneas that were stored in M K showed relatively normal cells with dense nuclei and cytoplasm The cells were normal in thickness The plasma membranes were intact and the mitochondria were mostly small and normal looking The intercellular membranes were intact with tight junctions and maculae adhaerentes Only a few vacuoles were seen in the endothelial cells stored in M K medium These were probably mostly mitochondria which had lost their inner structures Some vacuoles were also seen between the endothelial cells and Descemet's membrane The lateral membranes of the intercellular borders were closely apposed (Fig 3 A B)

In those corneas which had been cryopreserved for various times (frozen and thawed) a great variety of changes were seen in the endothelium In most cases the nuclei and the endoplasmic reticulum showed no changes On the other hand in almost all intercellular spaces the lateral cell membranes were separated so that there were empty spaces of various sizes between the cells (Fig A B) The cell membranes were intact and the cells were often attached to each other in one (tight junctions) or many places (maculae adhaerentes) Large vacuoles (enlarged mitochondria) were also found inside the cytoplasm Often the cell membrane was partly detached from Descemet s membrane and the same kind of spaces were found between the membrane and the endothelial cells as between the lateral borders of the cells

Discussion

According to numerous reports the cell density of the corneal endothelium decreases after several kinds of intra-ocular operations but endothelial loss even when heavy is not immediately disastrous for the cornea remains transparent with a very small number of endothelial cells (Bourne & Kaufman 1976, Bourne et al 1976a Bron & Brown 1974)

In this study I measured endothelial cell densities before and after keratoplasty and so evaluated the cell loss during excision preservation and surgical manipulation of the graft Counts were available for the exact numbers of endothelial cells of the donor or donors fellow eye corneas before keratoplasty and in the transplant about one year later The cadaver time with which cell loss is known to increase was minimal for all transplants The role of histocompatibility was minimal because patients had 0 1 mismatches and only 5 keratoconus patients had two mismatches So the most important factors responsible for cell loss were the type of preservation of the corneas the surgical manipulation and perhaps the age of the donors

During cataract extraction the corneal endothelium suffers damage when the cornea is bent (Norn 1971). In my study no endothelial cell damage was detected with vital staining in corneas stored in M-K medium so it seems that trephining the corneal button with a rotor trephine is harmless to the endothelium when done skilfully. Hence the cell loss seen in cryopreserved corneas after preservation presumably depends chiefly on the injury induced by dehydration, freezing and thawing.

Van Horn et al. (1969, 1972, 1973) made studies on the effect of cryopreservation on the ultrastructure of the endothelial cells. They concluded that during the cryopreservation method of Kaufman & Capella the viability of endothelial cells is maintained providing that the corneas are frozen within a few hours of the death of the donor. However, they found large intercellular spaces between the endothelial cells, which they attributed to the high osmolarity of the medium used for corneal cryopreservation, a solution containing dimethylsulphoxide, sucrose and albumin. Their study (Van Horn et al. 1969) showed that incubation of corneas in this medium led to distended intercellular spaces ... freezing and ... the spaces were no longer visible and the interc... were a... apposed.

In the present study I found ...
but the intercellular spaces ...
attached to each other only ...
morphological changes ...
grafts long after keratop...
the dehydrating ion pump ...
half the endothelial cel...
appear that most of the ch...
reversible, and that sooner ...
normal function.

SEM showed some cell l...
in lines or clusters of 5–10 ce...
the result of mechanical ...
disrupted cells the ...
endothelium appeared less ex...
cornea. This seems reasonabl...
looking in SEM no longer c...

References

W M & O Fallon W M (1978) Endothelial cell loss during penetrating keratoplasty *J Ophthal. 85* 760–766

•W M & Kaufman H E. (1976a) Specular microscopy of human corneal endothelium o *Amer J Ophthal. 81* 319–325

W M & Kaufman H E. (1976b) The endothelium of clear corneal transplants *A ch. hal. (Chicago) 94* 1730–1732

oill F S Polack F M & Slappey T (1973) A comparison of two methods of cutting or corneal buttons *Amer J Ophthal. 75* 500–506

L J & Brown N A P (1974) Endothelium of the corneal graft. *T ans. Ophthal. Soc 94* 863–873

a J A Kaufman H E. & Polack F M (19 2) Prognosis of keratoplasty in phakic and ikic patients and use of cryopreserved donor tissue *Trans amer Acad Ophthal ryng* 76 12 5–1985

a J A Kaufman H E. & Robbins J E. (1965) Preservation of viable corneal tissue *Ophthal. (Chicago) 74* 669–673

R. A Sandstrom H M Berrospi A R & Leibowitz H M (1976a) Morphological ges in corneal endothelial cells after penetrating keratoplasty *Amer J Ophthal 82* –464

R. A Sandstrom M M Berrospi A R. & Leibowitz H M (1976b) Changes in the eal endothelium as a function of age Exp Eye Res 22 587–594

A Cable M K Hoffman C. E. & Hanna C (1978) Endothelial cell population changes uman cornea during life *A ch Ophthal. (Chica o) 96* 2031–2035

ey B E. & Kaufman H E. (1974) Improved corneal storage *Invest. Ophthal. 13* –173

te D M (1968) Cellular membrane activity in the corneal endothelium of the intact *Experientia (Basel) 24* 1094–1095

M S (1971) Vital staining of corneal endothelium in cataract extraction. *Acta ophthal* L) 49 725–733

ns J E. Capella J A & Kaufman H E. (1965) A study of endothelium in keratoplasty corneal preservation *Arch. Ophthal. (Chicago) 73* 249–247

vaara P (19 9) Effect of corneal preservation donor age cada er time and postopera period on the graft endothelium *Acta ophthal (Kbh) 57* 868–881

Horn D L. Edelhauser H F Gallun A B & Schultz R. O (1972) Reversibility of astructural freeze-thaw induced injury *Arch. Ophthal. 87* 422–426

Horn D L. & Schultz R. O (1973) Endothelial survival in cryopreserved human corneas anning electron microscopic study *Invest. Ophthal 13* 7–16

Horn D L. Schultz R O & Edelhauser H F (1969) Corneal cryopreservation. rations in endothelial intracellular spaces *Amer J Ophthal. 68* 454–458

as M (1950) Remarks on technique of corneal transplantation *Amer J Ophthal. 33* Pt. 0–71

as S (1975) Excision of the donor cornea instead of enucleation *In est Ophthal 14* –795

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VITAL STAINING OF EXTERNAL EYE OF RABBIT
by Fluorescein Rose bengal Tetrazolium and Alcian Blue

BY

M S NORN

Fifty normal albino rabbits (Ssc CPH) had 1% fluorescein and 1% rose be...
instilled into the right eye and 1% tetrazolium and 0 5% alcian blue ...
left eye
The cornea was stained by fluorescein in no more than ...% by rose be...
frequently (48%) and intensely often over the area coverable by the ...
membrane and by tetrazolium correspondingly in 28%
Rosen bengal stained the nictitating membrane and often ... along ...
border
Marx line was seen to be regular festoon shaped Unlike the human ...
line that of the rabbit does not continue through the punctum lacrimale ...
3 mm behind the lid margin at the nictitating membrane The passage of ...
takes a few minutes
The alcian blue stained mucous thread resembled the human one
Percentage values and mean staining grades have been stated for the ...
regions

Key words vital staining fluorescein rose bengal tetrazolium alcian blue
lacrimal drainage system – nictitating membrane – Marx line – rabbit

It is a well known fact that we should be wary of drawing conclusions ... results of rabbit experiments to the clinical conditions in man Not least ... lens experiments experimental keratitis and trauma The external eye of ... differs in several important respects from that of man. The rabbit has ... almost ring shaped lacrimal gland It has only one punctum lacrimale ... mm behind the lid margin at the root of the semilunar fold. The ...

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oped into a nictitating membrane which may cover at least half of the cornea abbit very rarely blinks (Prince 1964)

may therefore expect to find vital staining properties in rabbit eyes differing from those in human eyes

object of the present investigation has been to compare the vital stainability rabbit eye with that of the human and in this connection to set up a normal ial of rabbits with regard to the most important dyes serving for vital staining external eye

Material

albino rabbits *(Oryctolagus cuniculus)* had both eyes vital stained The animals sent a cross breed between Danish country breed and ram rabbit from the ies closed colony since 1950 international term Ssc CPH Kept in single cages State Serum Institute Copenhagen

ights ranging from 2 to 3½ kg

Methods

right eye was vital stained by a mixture of 1% fluorescein and 1% rose bengal hen rinsed with a balanced salt solution (Alcon) (N = 50) The left eye was ed by a mixture of 1% tetrazolium and 0 25% alcian blue (N = 50) without equent rinsing (Norn 1974)

e rabbit calmed down and fixed by the keeper was examined *without* sthesia in Kowa s hand held slit lamp (magnification × 20) A cobalt filter was in front of the light source for fluorescein and white light for the other dyes staining was graded on the basis of the number of stained dots within the n concerned (cornea bulbar conjunctiva etc —vide legend to Table I) grades corresponding to <30 <100 <1000 <10 000 and >10 000 dots respectively

Results

l staining properties of the external eye of the rabbit differed from the human in the following respects

cornea was stained more often (Table I) and with a higher mean grade (Fig 1) ose bengal and tetrazolium (cf Norn 1970 1972) especially the entire medial or medio inferior half of the cornea, where the staining presented an upward

Table I

Vital staining of normal rabbit eyes (N = 50) The figures indicate the percentage of eyes stained within the region concerned C cornea B bulbar conjunctiva P nictitating membrane CA caruncle T inferior tarsus M Marx line on lower lid TS superior tarsus MS Marx line on upper lid MT mucosa of inferior fornix of conjunctiva.

	C	B	P	CA	T	M	TS	MS	M[illegible]
Fluorescein	2	0	0	8	0	0	0	0	
Rose bengal	48	2	92	84	2	100	[illegible]	[illegible]	[illegible]
Tetrazolium	28	2	6	8	8	16	[illegible]	[illegible]	[illegible]
Alcian blue	0	0	8	6	0	0	0	0	

and temporally convex curve sharply demarcated from the remaining [illegible] cornea

The vital stained area was identical with the region coverable by the [illegible] membrane The delimitation seemed to correspond to the edge of the [illegible]

The *nictitating membrane* was stained more often than the corresponding [illegible] fold of the human eye by rose bengal In 28% the more intense [illegible]

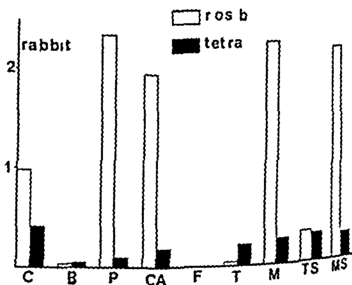


Fig 1

Vital staining of normal rabbit eyes by rose bengal and tetrazolium. Ordinate [illegible] grade (scales 1–5) Abscissa sites (for abbreviations see Table I)

ntrated particularly in the follicles located in a single row along the border of membrane In another 28% the staining was seen as a band along the brane border with no relation to follicles in 28% as diffuse punctate staining remaining cases as one or more horizontal bands

line along the lid extended as forward bulging festoons of rose bengal stained the outlets of the Meibomian glands often in several rows backwards arrangement was far more regular than in human eyes where the outlets often much less regularly located

arx line was seen not to continue through the punctum lacrimale into the liculus as it often does in man The rabbit s punctum lacrimale is situated 3 mm nd the lid margin This region was not stained at all and Marx line remained hanged in the neighbourhood of the punctum lacrimale

ose bengal and alcian blue dye passed out of the nose few minutes after the llation In humans with a normal function this does not occur until 15–30 min

us was stained rarely but more often by tetrazolium compared with normal ian eyes

mucous thread was stained by alcian blue and tetrazolium like humans In only cases did the red colour predominate as a sign of bacterial infection (cf Norn 4) In one of these the keeper had diagnosed inflammation of the eye prior to vital staining

nters fluorescein pattern was not detectable by rubbing nor by using Perkin s ometer with positive pressure Such has always been provokable in man (Norn 68) The difference is due to absence of Bowman s membrane in the rabbit

Discussion

e present series of 50 rabbits may be regarded as a normal material the rabbits ng well-cared for in single cages with no signs of corneal lesions (only one case of orescein stainability) or infection (though two with mucous thread staining ggesting infection)

Rabbit corneae were frequently stained by rose bengal presumably owing to esence of the nictitating membrane which in itself presents peculiar staining tterns The festoon shaped Marx line and the lacrimal drainage system with its pid outflow likewise differ essentially from the conditions in man To these may added a series of minor differences indicating that experience gained from iman eyes is not directly transferable to rabbit eye material nor vice versa

Acknowledgments

I wish to thank the staff of the Veterinary Unit the State Serum Institute fo assistance

References

Norn M S (1968) Schweitzers polygonal fluorescein pattern on cornea. Ac
46 700–711

Norn M S (1970) Rose bengal vital staining *Acta ophthal (Kbh)* 48 546–559

Norn M S (1972) Tetrazolium Alcian blue mixture *Acta ophthal (Kbh)* 50 9

Norn M S (1974) External Eye Methods of Examination p 200 Scriptor Cope

Norn M S (1979) Semiquantitative interference study of fatty layer of pre
Acta ophthal (Kbh) 57 766–774

Prince J H (1964) The rabbit in Eye Research p 652 Charles C Thomas Spri

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A MEDICATION MONITOR AND FLUORESCEIN TECHNIQUE DESIGNED TO STUDY MEDICATION BEHAVIOUR

BY

S E NORELL[1] P A GRANSTRÖM[2] and R WASSEN[3]

Methods were developed to study medication behaviour in order to obtain accurate and detailed information on the patterns of drug taking in medication with eye drops A medication monitor was designed which recorded the date and hour each time the medication bottle was opened A fluorescein technique was designed to study the ability of patients to administer the eye drops into the conjunctival sac Some problems in the measurement of medication behaviour are discussed In a group of patients with open angle glaucoma for whom pilocarpine eye drops three times daily had been prescribed 18% of dose intervals had a duration of 12 h or more and 11% had a duration of 4 h or less Fluorescein tests indicated that the patients were usually able to administer the eye drops correctly

Key words medication – patient compliance – pilocarpine – glaucoma.

recent years much attention has been paid to patient compliance in general and ...dication behaviour in particular Several studies have shown that about 50% of ...ients on long term medication do not follow the prescribed regimen Higher or ...er percentages have been found e g in different patient populations and with ...ferent drug regimens (Sackett 1976)

Two major problems in studies of medication behaviour are related to measure...nt methods Firstly the accuracy has been shown to be unacceptably low for ...me of the most commonly used methods including interview (Bergman & ...erner 1963 Gordis et al 1969 Roth & Caron 1978) Secondly most of the ...ethods used offer only very rough measures of the patterns of drug taking such

...ceived September 24th 19 9

as the average number of missed doses However the effect of dr g is not only related to the number of doses taken but also to the spacing betw

Different objective methods have been used to study medication be. Among these a medication monitor technique may offer the most information on the patterns of drug taking A source of radioactive mar photographic film was used by Moulding to monitor self medication with culostatic drugs (Moulding 1962 Moulding et al 1967) and oral (Moulding 1971) A medication monitor for eye drops was described by (1974) The use of a medication bottle was recorded by an electronic system provided that the patient replaced the medication bottle container each time it had been used This monitor was only used to medication behaviour of two patients (Yee et al 1974)

For some patients and drug regimens there may be difficulties in adm the drug correctly This problem is often neglected in studies of co



Fig 1
Medication monitor with a 25-ml bottle for eye drops

iour Nevertheless it may be worth considering for example in medication eye drops among elderly people As far as we know no studies have been ished on the ability of patients to administer eye drops into the conjunctival sac e purpose of the present study was to develop methods to measure medication viour in order to obtain accurate and detailed information of the patterns of taking in medication with eye drops

Material and Methods

dication monitor was designed which recorded the date and hour each time the ication bottle was opened The monitor (Fig 1) consists of a plastic box suring 100 × 50 × 25 mm with a holder for a 25 ml medication bottle The er is designed to protect the bottle and to facilitate replacement of the dropper cap An elastic flap linked to a micro switch inside the box signals to the tronic part of the monitor whether the cap is on or off A sliding lid in the om of the monitor can be removed for exchange of bottle and battery (Fig 2) lid is sealed when the monitor is used

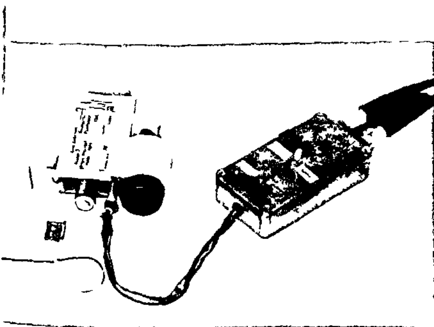


Fig 2
Medication monitor with read-out device Sliding lid and actu ating plug remo ed

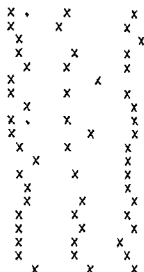


Fig 5

Monitor record describing 20 days of tid medication Each line represents 24 h [illegible] on each line representing the first hour after midnight and so forth Each X [illegible] pulse indicating that the medication bottle was opened

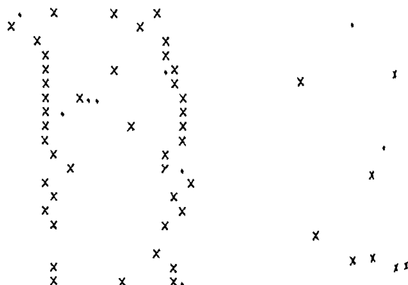


Fig 6

Monitor records of two patients for whom pilocarpine eye drops three times da[illegible] prescribed For interpretation see legend for Fig 5

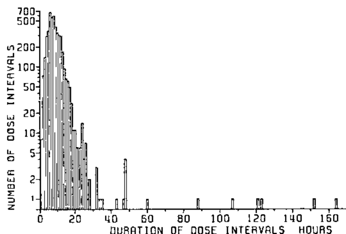


Fig 7

ency distribution of dose intervals in hours during a 20-day period for 82 patients for whom pilocarpine eye drops three times daily had been prescribed

Results

of the display from the monitor by an ECG recorder is shown in Fig 4 The from Fig 4 were fed to a computer and expressed on the first three lines of) together with the following 17 lines covering a 20-day period Similar data two other patients are shown in Fig 6 Monitor data on the duration of dose vals from all 82 patients are given in Fig 7 The intervals varied from 1 to 164 h a mean of 8 7 h and a maximum frequency at 6 h Of the dose intervals 840) had a duration of 12 h or more and 509 (11%) had a duration of 4 h or less rescein tests were all positive except in one patient who had two negative tests

Discussion

he interpretation of medication monitor data some problems should be idered For example there could be variations in medication behaviour related he design of the medication bottle and the duration of intervals between clinic s

capacity of the monitor is limited to about three weeks and therefore the rvals between clinic visits will be shorter than usual for most patients

he possibility of removing the drug from the bottle for consumption on a later asion should be considered in medication with pills However in studying

medication with eye drops this is not likely to be an important [illegible] variations in the number of doses taken on one occasion seem [illegible] importance in medication with eye drops (Duke Elder 1962)

The fluorescein tests showed that with one exception our patients [illegible] administer the eye drops correctly This finding indicates that the [illegible] supply information on dose intervals provided that the bottle was not [illegible] some purpose other than trying to take the drug and that the patients [illegible] access to other sources of the drug

During the time we have used the medication monitor there were [illegible] technical problems In a few cases however a monitor record was [illegible] after a second 3 week period owing to defective monitor batteries [illegible] test period For practical reasons the medication monitor is used [illegible] research purposes on a relatively small scale Furthermore the [illegible] medication monitoring deserve further attention

We believe that the medication monitor and fluorescein techniques [illegible] valuable information on medication behaviour since they offer data on the [illegible] of drug taking by date and hour Such information could be an [illegible] towards understanding and improving medication behaviour

Acknowledgment

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References

Bergman A B & Werner R J (1963) Failure of children to receive penicillin [illegible] *Engl J Med 268* 1334–1338

Duke Elder S (1962) System of Ophthalmology Vol VII The Foundations of [illegible] logy p 502 Henry Kimpton London

Gordis L Markowitz M & Lilienfeld A (196[illegible]) The inaccuracy in [illegible] estimate patient reliability in taking medications at home *Med Ca[illegible]* [illegible]

Moulding T (1962) Proposal for a time recording pill dispenser as a [illegible] and supervising the self administration of drugs *Amer Rev Resp Dis* [illegible]

Moulding T Knight S J & Colson J B (1967) Vertical pill-calendar [illegible] medication monitor for improving the self administration of drugs *[illegible]* 32–37

Moulding T (1971) The medication monitor for studying the self administration [illegible] contraceptives *Amer J Obstet Gynec 110* 1143–1144

Roth H P & Caron H S (1978) Accuracy of doctors estimates and patients [illegible] adherence to a drug regimen *Clin Pharm Ther 23* 361–370

D L. (19 6) The magnitude of compliance and non-compliance In Sackett D L. &
ɜ ıes R. B (eds) Compliance with therapeutic regimens pp 9-25 Johns Hopkins
ersity Press Baltimore & London
D., Hahn P M & Christensen R E. (1974) Medication Monitor for Ophthalmology
J Ophthal 78 774 778

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REFRACTION NEARWORK AND EDUCATION

A Population Study in Newfoundland

BY

AVRUM RICHLER and JOHN C BEAR

There is little information directly relating ocular refraction and near[illegible] habits in representative human populations Ocular refraction (diopters), nearwork (hours per day) and education (years) were therefore measured in 957 persons comprising 80% of the population aged 5 years and over of [illegible] communities in western Newfoundland Refraction was moderately consistently and significantly correlated with nearwork from ages 5 to 14 and remained so after adjustments for the association of refraction and nearwork levels with age sex and education Multiple regression coefficients relating refraction to nearwork decreased from −0 13 D/h at ages 5-14 years to [illegible] D/h at ages 60 years and up The magnitude of this association, and its consistency and persistence over a wide age range suggest that large amounts of nearwork in childhood may contribute to the prevalence of clinical myopia

Key words refraction – nearwork – education – population study – epidemiology

Ocular refraction in man is a continuously distributed attribute usually [illegible] arbitrarily into myopia emmetropia and hyperopia Its distribution [illegible] roughly normal but leptokurtotic with a mean and mode in low [illegible] hyperopia and a deficiency in the low myopic range (Goldschmidt 19[illegible]) [illegible] the distribution is markedly leptokurtotic still exhibiting a mean and mode [illegible] hyperopia but also a pronounced skew to myopic values (Betsch 1929).

Myopia of clinical degree usually becomes manifest in late childhood [illegible]

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in degree for some years thereafter (Duke Elder 1970) In its higher degrees ia is of particular importance because it can often progress to blindness High ia is usually pathological rather than an extension of normal variation in ction (Francois 1961 Duke Elder 1970) Lesser degrees of myopia are also of considerable social and economic importance Over half the population of the over the age of 6 years wear corrective lenses of these about half wear lenses cting for myopia Nearly 90% of corrections worn by those between the ages and 27 years are for myopia (National Center for Health Statistics 1978)

he complexity of the eye and of its refractive elements is such that its growth development must be under elaborate genetic control emmetropia which rs more often than would be expected were refraction normally distributed lts from correlated growth of cornea and lens adjusting for elongation of the axis (Sorsby et al 1961) Resemblances between relatives suggest a substantial tic component in population variation in ocular refraction (Sorsby et al 1962)

n the other hand the morphological variations underlying substantial refraction rences is very small An uncompensated excess of 1 mm i e 4% in the length he optic axis which averages 24 mm in adulthood implies a myopia of −3 ters Only about 10% of the U S population are as shortsighted or more so tional Center for Health Statistics 1978) Subtle environmental disturbance of lar development might therefore markedly influence refraction

here is experimental evidence that in accommodation the process by which the adjusts to near viewing the tension on the choroid is increased (van Alphen 1) and it has been postulated that a resulting increase in intraocular pressure ses the optic axis to elongate and the eye to become myopic (Young 1975) Thus s reasonable to postulate that variation in nearwork levels among the young ld through the influence of accommodative effort on axial length contribute to pulation variation in ocular refraction

There is relatively little information relating ocular refraction and nearwork its in representative unselected human populations In Danish male conscripts opia is clearly associated with occupational and educational background more icated groups having a higher frequency of myopia and this association has rsisted over the last 80 years (Goldschmidt 1968) Myopia is more common in nish children in academic as opposed to other school streams (Goldschmidt 68) and in British children of non manual as opposed to manual workers ckham et al 1977) Genetic heterogeneity of these populations along social class es may be at least suspected of confounding these observations (Goldschmidt 68)

In view of the lack of direct observations in this area and because of its potential portance an investigation was undertaken relating the ocular refraction educa

tion and nearwork habits of inhabitants of 3 rural Newfoundland c... Familial resemblances in refraction and in nearwork habits were ... results of these studies are reported elsewhere (Bear & Richler ... publication to J. biosoc. Sci.)

Subjects and Methods

The population studied resides in 3 communities situated within ... another on the west coast of Newfoundland and is historically and ... stable with little immigration. Data were collected in 1974.

Ocular refraction was determined in the course of a standard ... examination of each subject (Borish 1970). All refractions were perform... same observer (AR). A fogging lens was used to relax accommodation ... was evaluated with the retinoscope and refined subjectively both ... binocularly as the minimum concave or maximum convex lens ... required to give a distance acuity of 20/20. For purposes of the present ... required cylindrical correction was converted to spherical power ... meridian and because right and left eye refractions are highly correlated ... in this series $P < 10^{-5}$) only right eye refractions were analyzed.

Nine hundred and seventy-one (971) persons aged 5 years or over ... refracted about 80% of the total population above that age. All subjects ... for examination were refracted; subjects were not selected on visual ... Eleven persons with myopia greater than −6D were excluded from f... because of the high probability that their myopia was pathological. Thre... with right eye amblyopia were also excluded. The population and ... distribution of refraction are described elsewhere (Richler & Bear 1980).

Nearwork was measured as h/day as reported by the subject spent ... such as reading, sewing or knitting requiring focussing of the eyes at a ... 20 inches or less. This measure is clearly approximate and depends upon ... of recall and the habitual attentiveness of subjects to nearwork tasks. The ... persons to whom this analysis relates comprise 388 young school ... housewives, 106 fishermen, 44 men occupied in farming, forestry or ... men working in construction trades or as truck drivers, 25 sales clerks, ... as bookkeepers, health personnel, draftsmen or mechanics, 14 teachers ... plant workers, and 26 persons giving no occupation. It can be appreciated ... a small proportion of the population were engaged in occupations ... moderate amounts of close work or reading.

Education was measured in years as last completed grade. Formal ... effectively became compulsory only after the confederation of New...

la in 1949 a change affecting persons aged 30 years and under at the time of
nvestigation. Many subjects above middle age had little or no formal education.
have returned to school for upgrading in primary education grades so
leted are included in the education measure
e was calculated as (year of investigation) – (year of birth) sex coded for
sis as 1 = male 2 = female
ble I presents means and standard deviations of refraction nearwork and
ation by five year age intervals Refraction means trend to more negative
pic) values between the age of 5 and 15 years trend to more positive
eropic) values from age 20 to age 59 and take an erratic course at higher ages
ew of this pattern and of the introduction of compulsory education in 1949
population was divided in 5 groups by age 5-14 15-29 30-44 45-59 and 60
s and up The relationship of refraction to the other variables and to sex was
examined in each of these age intervals

Results

le II presents the simple correlation coefficients relating refraction to age sex,
cation and nearwork in each of the 5 age intervals (It may be noted that since
es of *negative power correct for myopia negative correlations with refraction*
ly a positive association with nearsightedness)

The numerous significant correlations are for the most part explicable The
dency to myopia in the first age interval is generally observed as is a gradual
dency toward hyperopia after that period (Duke-Elder 1970 National Center
Health Statistics 1978) The positive associations of education and nearwork
h age in the youngest group result from school attendance among persons aged
to 59 the association of education with age is negative because only rudimentary
mal education was available to the older subjects The association of education
d nearwork is hardly surprising Associations of nearwork and sex probably
licate greater interest in school and home activities among young girls than
ung boys and time spent in knitting and sewing by older women The association
refraction with sex in the 15-29 year group indicates a generally observed sex
fference in age changes in refraction the shift to negative refractions with age
curring earlier in females than males and being somewhat greater (Young et al.
54 Sorsby et al 1961 Goldschmidt 1968)

Most striking is the consistent association of refraction with nearwork until age
) This association is maintained despite a reversal in the relationship of nearwork

Table I
Age distribution of refraction nearwork and education

Age interval	n	Refraction		Nearwork		Ed[illegible]
		mean	SD	mean	SD	mea[illegible]
5–9	195	−0.620	1.026	0.646	0.814	[illegible]
10–14	145	−0.172	1.251	1.455	1.040	[illegible]
15–19	108	−0.924	1.472	1.796?	[illegible]	[illegible]
20–24	76	−0.812	1.619	1.461?	1.478?	[illegible]
25–29	85	−0.286	1.722	1.471	1.411	[illegible]
30–34	53	−0.094	0.935	1.434	1.394	[illegible]
35–39	49	0.082	0.967	1.704?	1.479?	[illegible]
40–44	55	0.236	1.409	1.200	1.830?	[illegible]
45–49	52	0.533	1.477	[illegible]	1.309	[illegible]
50–54	48	0.765	0.894	0.771	1.219?	5.23?
55–59	25	0.747	0.706	0.850?	[illegible]	4.84?
60–64	28	1.414	1.595	0.393	0.567?	[illegible]
65–69	18	1.442	1.445	1.056	1.259	[illegible]
70–	20	0.758	1.808	0.850	0.875?	[illegible]

to age in the teenage years and despite the more gradual but even great[illegible] in the relationship of education to age

In the oldest group senile lens changes affect refraction in some cases [illegible] and the smaller number of subjects may account for the general weak[illegible] associations between variables after age 60

Partial correlation coefficients (Table III) indicate that the confound[illegible] age and sex inflate somewhat the simple correlation of nearwork and re[illegible] the 5-14 year interval but not at higher ages and suggest the associat[illegible] education with refraction can account for some of the association of near[illegible] refraction The association of refraction with nearwork remains significant [illegible] 60 after statistical adjustment of both variables for their association with [illegible] and education

Multiple regression equations (Table IV) were calculated in each age interva[illegible] determine the proportions of population variance in refraction that [illegible] independently attributed to differences in each of the other variables The [illegible] refraction variance was not accounted for by this analysis at any age For p[illegible] aged under 60 years education and nearwork taken together account for [illegible] proportions of refraction variance and very substantial proportions of r[illegible]

ınce Because education and nearwork are correlated the proportions of ained variance allotted to each depend on the order in which they are entered ie regression equations When entered before education nearwork accounts for e variation than education in each age group (data not shown)

Table II

Correlations among refraction and other ariables

	Age	Sex	Education	Nearwork
s 5 14 (n=340)				
efraction	–0 374	–0 081	–0 399	–0 4 2 *
Age		0 040	0 962* *	0 409 *
ex			0 074	0 2'6 *
Education				0 452 **
es 15 29 (n–269)				
Refraction	0 176	–0 215	–0 21	–0 33 ***
Age		–0 049	–0 036	–0 114*
Sex			–0 059	0 056
Education				0 313***
es 30-44 (n–157)				
Refraction	0 109	0 007	–0 384	–0 489* *
Age		–0 041	–0 353 **	–0 121
Sex			–0 049	0 006
Education				0 461
ges 45 59 (n=125)				
Refraction	0 198	0 015	–0 187	–0 358 *
Age		–0 209	–0 299* *	–0 097
Sex			0 067	0 162
Education				0 534 *
ges 60 (n=66)				
Refraction	–0 238	0 166	0 007	–0 098
Age		0 140	0 190	0 263*
Sex			0 033	0 221
Education				0 496 *

$P < 0\ 05$ $P < 0\ 01$ $P < 0\ 001$

Table III
Partial correlations of refraction and nearwork

Age interval	Simple r	Controlling for age and sex	[illegible]
5 14	−0 472	−0 371**	−0 331
15 29	−0 332	−0 310*	[illegible]
30-44	−0 189	−0 492**	[illegible]
45 59	−0 258	−0 259**	[illegible]
60-	−0 098	−0 082	−0 111

* $P < 0$ 05 ** $P < 0$ 01

Discussion

Present findings clearly indicate in the population studied an [illegible] refraction and an admittedly approximate nearwork measurement. The [illegible] however whether this association indicates that nearwork actually [illegible] refraction For instance it has been plausibly argued by Goldschmidt [illegible] the association of myopia with education and occupation in the [illegible] structure of Europe is the result of prolonged genetic selection and stratification On the other hand the prevalence of myopia in Eskimo and [illegible] populations seems to have increased dramatically with the introduction of education (Young et al 1969 Woodruff & Samek 1977) at a rate far [illegible] that sustainable by genetic mechanisms

What social and economic differences exist in the population [illegible] relatively minor as indicated by the distribution of occupations [illegible] settled nature of the population lack of recent immigration and [illegible] genetic analyses (Marshall 1976) suggest it to be relatively homogeneous [illegible] The observed associations of refraction with nearwork and education are [illegible] not easily explained in terms of underlying social or genetic variation.

The persistence and relative stability of the association of [illegible] nearwork in each age interval and the strikingly parallel age trends of [illegible] (Fig 1) despite reversals in the relationship of each with age [illegible] association is not artifactual It cannot be argued that increasing levels of [illegible] in this population have increased the average person s nearwork [illegible] manner which happens by chance to parallel age changes in refraction [illegible] be seen in any case because as shown in Table III the association [illegible]

Table IV
Multiple regression of refraction on other variables

Age interval	Independent variables	Multiple correlation	Variance described (r^2 change)	Regression coefficient	Standard error
-14	age	0.3739	0.1398	0.0072	0.0754
	sex	0.3797	0.0044	0.0492	0.1154
	education	0.4035	0.0187	-0.1138	0.0806
	nearwork	0.5159	0.1033	-0.4332	0.0631
	constant			1.0522	
15-29	age	0.1756	0.0308	0.0480	0.0204
	sex	0.2713	0.0428	-0.6628	0.1908
	education	0.3519	0.0503	-0.1257	0.0513
	nearwork	0.4260	0.0576	-0.3007	0.0698
	constant			1.1918	
30-44	age	0.1094	0.0120	-0.0027	0.0188
	sex	0.1100	0.0001	-0.0022	0.1588
	education	0.3851	0.1362	-0.0801	0.0324
	nearwork	0.5208	0.1229	-0.2868	0.0567
	constant			1.2662	
45-59	age	0.1280	0.0164	0.0316	0.0236
	sex	0.1348	0.0018	0.1828	0.2067
	education	0.2061	0.0243	-0.0094	0.0378
	nearwork	0.2903	0.0418	-0.2294	0.0980
	constant			-0.9424	
60-	age	0.2384	0.0568	-0.0536	0.0274
	sex	0.3123	0.0407	0.7367	0.4067
	education	0.3126	0.0008	0.0464	0.0737
	nearwork	0.3307	0.0110	-0.2248	0.2588
	constant			3.6548	

adjustment for the effects of age and education on refraction and nearwork level. Since it is highly improbable that in the population studied persons of all ages are carefully adjusting their generally low nearwork levels to their refractions, these findings strongly suggest that nearwork does indeed influence refraction in a myopic direction. The exclusion of 11 subjects by virtue of their unusually high myopia does not affect the observed association of myopia with nearwork: these persons had on average more education (10.18 years) and did rather more nearwork (2.82 h daily) than the rest of the subjects.

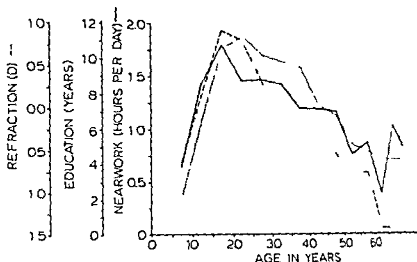


Fig 1

Course of 5 year age group means of refraction nearwork, and [illegible]

It is not possible in cross sectional data to approach the question [illegible] nearwork levels decrease refraction in all young persons or only some [illegible] longitudinal studies indicate that most children show increases in axial [illegible] age the rate of elongation being variable Such elongation uncom[illegible] correlated cornea and lens growth is the principle cause of myopia Com[illegible] growth of cornea and lens does however usually occur again to vary[illegible] and emmetropia is usually fairly well maintained Compensation is less complete when the rate of axial elongation is high (Sorsby et al [illegible] variation in growth of the ocular components is superimposed on the [illegible] refraction which has some influence on the refraction measured in late [illegible] childhood (Sorsby et al 1961 Hirsch 1964) The large excesses of [illegible] observed among Eskimo and Amerind students by comparison with [illegible] suggest that levels of nearwork usual to North American education may [illegible] the refractions of most young persons

The regression values relating refraction to education and nearwork [illegible] population (Table IV) should be cautiously interpreted *In the individual* [illegible] normally changes only gradually after late adolescence The [illegible] regression coefficients relating refraction with nearwork in each age [illegible] (IV) cannot be taken to imply that for members of this population [illegible] amount of nearwork each day will on average decrease refraction by the amount regardless of the age at which the nearwork is undertaken. The [illegible]

ult and younger nearwork associations with refraction is more likely to indicate personal nearwork levels are indeed habitual established in childhood and scence and that their effect on refraction is permanent Pending confirmation e findings of the present investigation in studies elsewhere the regression icients observed should not be extended to other nearwork levels in other ulations The magnitude of these regressions −0 3D per h of nearwork implies higher levels of nearwork in childhood and adolescence may have clinically r considerable effects on refraction particularly in cases of moderately high pia In particular longitudinal and family studies might clarify the generality herwise of the nearwork refraction association

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References

sch A (1929) Uber die menschliche Refraktionskurve *Klin Mbl Augenheilk 82* 365–379
nsh I (1970) Clinical Refraction Third edition Professional Press Chicago
ke Elder S (1970) Ophthalmic Optics and Refraction System of Ophthalmology Vol V
Mosby Company St Louis
ancois J (1961) Heredity in Ophthalmology C V Mosby Company St Louis
ldschmidt E (1968) On the Etiology of Myopia *Acta ophthal (Kbh.)* Suppl 98
ldschmidt E (1969) Refraction in the newborn *Acta ophthal (Kbh) 47* 570 578
rsch M J (1964) Predictability of refraction at age 14 on the basis of testing at age 6
nterim report from the Ojai longitudinal study of refraction *Amer J Optom. 41* 567–573
arshall W H (1976) The West Coast Health Survey Memorial University of Newfound
land St John s
ational Center for Health Statistics (1978) Refraction Status and Motility Defect of Persons
4-74 Years United States 1971 1972 (DHEW Publication No (PHS) 78-1654) Hyattsville
MD
eckham C S Gardiner P A & Goldstein H (1977) Acquired myopia in 11 year old
children *Brit Med J I* 542 544
chler A & Bear J C (1980) The distribution of refraction n three isolated communities in
western Newfoundland *Amer J Optom. & Physiol Optics* in press
orsby A Benjamin B & Sheridan M (1961) Refraction and its Components During the
Growth of the Eye from the Age of Three (Medical Research Council Special Report Series
No 301) Her Majesty s Stationery Office London

Sorsby A Sheridan M & Leary G A (1962) Refraction and its Components (Medical Research Council Special Report Series No 303) Her Majesty's [illegible] London

Sorsby A Leary G A & Fraser G R (1966) Family studies on ocular [illegible] components *J Med Genet 3* 269–273

van Alphen G W H M (1961) On Emmetropia and Ametropia *[illegible]* Supplementum

Woodruff M E & Samek M J (1977) A study of the prevalence of [illegible] refractive states and anisometropia in Amerind populations in Ontario *Can J [illegible] 68* 414–424

Young F A (1975) The Development and control of myopia in human and [illegible] primates *Contacto 19* 16–31

Young F A Beattie R J Newby F J & Swindal M T (1954) The Pullman [illegible] survey of Pullman school children *Amer J Optom 31* 19?–203

Young F A Leary G A Baldwin W R & West D C (1969) The transmission of [illegible] errors within Eskimo families *Amer J Optom 46* 676–685

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he Ophthalmologische Gesellschaft Bericht uber die 75 zusammenkunft in Heidelberg 1977 Kunststoffimplantate in der Ophthalmologie Editor W Jaeger J F Bergmann Verlag Munchen 1978 717 pages.

than 200 papers from the German ophthalmological society meeting in Heidelberg are presented in this book. Of the numerous papers 75 deal with the specific topic for meeting Some papers discuss the pure technical aspects of polymers and plastics, others ssue reaction to these materials from a clinical point of view Great interest is also paid to ocular lenses

ch discussions finishes by dealing with some aspects not mentioned in the papers It is *pointing that one of the greater complications with intraocular lenses, namely endo*al distrophy is only mentioned in one sentence

ie useful application cyanoacrylate adhesives in detachment surgery and in combination contact lenses is beautifully presented in several papers The results in detachment ery using various implants are presented in 12 papers

ne main topic for the conference is completed with a discussion on iris-clip-lenses and capsular lenses in 20 pages with the very experienced pioneers in this field

is not possible in a brief review to mention the free papers It is sufficient to emphasize almost any field in ophthalmology is presented

his book with the many free papers can be recommended to any ophthalmologist.

T ben So ensen

al Handicap in Child en. Vernon Smith & John Keen eds. Clinics in Developmental Medicine No 73 Spastics International Medical Publications with W Heinemann 19 9 172 pages Price U K Pds 8 00

e Spastics Society in 1976 sponsored a meeting on the isually handicapped children The nmunications of the meeting have been published in this volume The contents are as tinent today as they were in 1976 and contain the most up-to-day statistics on isual pairment in childhood

The last report by the late Dr Mary Sheridan concerning assessment of vision in small ildren and *infants is also included and is as clear and persuasive as anything she has* esented.

In fact, most problems concerning blind and partially s ghted children are discussed such causes of blindness common complications genetics of the most prevalent causes of isual ipairment, development of normal vision developmental psychology of children with ficient vision and how this effects the teaching of the visually impaired.

The present trend of integrated education has allowed educationally subnormal children to ter the previously very *competitive schools for the blind and* several authors discuss visual andicaps among mentally retarded children It will astonish some that 70% of blind ildren are multihandicapped.

The volume ends with a short but intense and comprehensive chapter by a mother to two sually retarded and one unaffected child This chapter at least, should be read by erybody in charge of visually handicapped children or their families. In unsophisticated hrases Mrs Matthews explains why parents must have a diagnosis genetic counselling and ducational advice as early as possible and that is what the rest of the volume is all about.

Mette Wa burg

A F Deutman and J R M Cruysberg Neurogenetics and Neuro-ophthalmology ... national Congress Nijmegen The Netherlands September ... 1977 ... by Publishers The Hague Boston London 19 8 486 pages ...
Price Dutch Guilders 165 – US dollars 84 –

At the 5th international congress of neurogenetics and neuro-ophthalmology ... September 1977 the main topics were myasthenia gravis optic atrophy and ... degenerations Furthermore there were free lectures on neuro-ophthalmological ...

The first section of the book deals with myasthenia gravis and begins with ... Huber Ocular myasthenia diagnosis and treatment In the subsequent articles ... of the disease are discussed – such as histology and histochemistry ... myasthenia gravis – the treatment and finally the important genetic ...

The next 100 pages deal with diseases of the optic nerve and chiasma ... articles by J Francois and W Jaeger on the hereditary optic atrophies. In this ... book the various authors have also stressed the importance of the examination ... diseases of optic nerve and chiasma Among other things van Lith & Henkes ... value of visual evoked cortical response in optic neuritis and tumours which ... the visual pathways

In the next passage there are excellent articles about the hereditary ... retinal diseases

The final passage comprises a number of articles with quite different neuro... gical topics

On the whole the articles of the book are well written and it must also be ... many of them have an extensive and adequate bibliography enabling the re... interested in these subjects to obtain considerable information The book ... to neuro-ophthalmologists and to those concerned with genetics and with the ... retinal diseases The book should find a place in the library of both eye and ... departments

Sensory Ecology Review and perspectives edited ... M A Ali Plenum Press ... London 1977 597 pages Price U S dollar ... 40

This extensive book is vol A18 in Nato Advanced study institute series ... nearly all the lectures from a congress in Canada July 1977

The subject is the organ of vision and the evolution of other organs illustra... various studies including comparative anatomic ... electro-physiological and ... visual patterns and also from an ecological standpoint One is overwhelmed ... the sensory organs the well-disposed experimental techniques and the many ...

Unicellular organisms with a markedly developed eye organelle are describe... and birds can register polarised and ultra violet light snakes can ... There is a description of the parietal eye secondary adaption of the terrestr... an aqueous existence echo sense electrical sense magnetic sense hygro se... The sense of smell is strongly developed e g in salamanders the marke... Lunar neurohormones and the song of the grasshopper are other fascinati...

The material is presented in 19 well-defined chapters with few but ... Each chapter is concluded with a status and a suggestion as regards future re...

The book ends with an extensive 60 pages index

The book can be recommended to anyone wishing to become orientated ... advances in the research of these exciting and amusing topics

E e Pa hol gy In t tute (Head O A Jen sen) Unn ers ty f C penha en
D partment of Op hnalmology (Head E Gregers n) R gsh pitalet C pe ha en
and r t f Oph hal n l gy (Head P B andstrup†)) H ido re Ho p tal H ido re Denmark

HUMAN SENILE CATARACT

Light and electron microscopic studies of the morphology of the anterior lens structures with special reference to anterior capsular/subcapsular opacity

BY

O A JENSEN and A B LAURSEN

Light and electron m croscop c stud es of human senile cataractous lenses w th and without b om croscop cally detectable anterior capsular subcapsular opacity (ACSCO) re ealed the ma n difference between the two types of cataract to be n the subep thelial cortex where ACSCO lenses showed dis ntegrating cortex f bres f bres of the deep cortical type and e en in some cases collapsed f bres These findings were cons dered to be associated w th the decompos tion and disappearance of the superf cial cortex n ACSCO lenses Numerous m tochondria n the ep thelium of ACSCO lenses po nt towards a h gh oxidat e metabolism wh ch may facilitate act e transport across the ep thelium
No d fference n capsular surface morphology between cataractous lenses w th and w thout ACSCO was found b scann ng electron m croscopy Transmiss on electron m croscopy showed n bo h categories of lenses granular inclus ons in the capsules most pronounced n totally opaque lenses
Large ntercellular vacuoles were seen in the anterior part of the epithelium both l ght and electron microscopically in both ca egories Consequently these ultrastructural changes do not seem to form part of the biomicroscop cal p cture of ACSCO Based on our study we prefer the term ASCO (anterior subcapsular opacity) n place of ACSCO the latter term ha ing been used by us pre iously

Key words cataract human sen le b om croscopy opacity anterior subcapsular (ASCO) m croscopy l ght and electron cortex f bres subep thelial – degeneration

Rec ei ed January 15th 1980

A *biomicroscopically visible* opacity located on the anterior aspect of [illegible] and characterized by the occurrence of vacuoles was reported by [illegible] Vogt (1914) Seen in the slit lamp this opacity (so far called by us [illegible] *capsular/subcapsular opacity*) appears as numerous capsular or sub[illegible] vacuoles so that the anterior aspect of the lens may even [illegible] appearance (Bruun Laursen 1976) The occurrence of ACSCO [illegible] nantly – though not exclusively – in the most opaque lenses ([illegible] Laursen 1977 Bruun Laursen & Fledelius 1979) has never been found [illegible] isolated phenomenon in senile lenses

Senile cataractous lenses with ACSCO – *in contrast to cataractous lenses* [illegible] it – are associated with physical and biochemical abnormalities such as [illegible] (Bruun Laursen & Fledelius 1979) low whole lens ribonucleotide [illegible] Laursen 1976) and high $C_{Na}+$ *and low* C_K+ *in whole lens water* ([illegible] Laursen 1977)

The aim of the present study was to investigate the [illegible] ACSCO and also to find an appropriate name for the phenomenon The [illegible] carried out by means of a) light microscopy (LM) b) transmission [illegible] microscopy (TEM) and c) scanning electron microscopy (SEM)

Material and Methods

The study comprised 32 lenses from 31 patients with uncomplicated senile [illegible] varied from 62 to 87 years Fourteen lenses had immature cataract with ACSCO [illegible] immature cataract without ACSCO and six lenses were totally opaque with [illegible] LM and TEM were performed on all lenses whereas SEM was performed [illegible] followed by the two other procedures

Biomicroscopical evaluation was performed according to Bruun Laursen [illegible] mydriasis 1 3 days before operation slit lamp photos being taken The lenses [illegible] extracted in retrobulbar anaesthesia The cataract extractions were [illegible] α-chymotrypsin was not used The frozen extraction area was marked [illegible] The lenses were rinsed in 0 9% saline and immediately placed in fixative [illegible] lens remained for 4 24 h The following fixatives were used at [illegible] glutaraldehyde (3 lenses) 4% glutaraldehyde ([illegible] lenses) and equal parts of 1% [illegible] de + 2% formaldehyde (8 lenses) All fixatives were buffered with 0 [illegible] pH 7 2

The part of the lens to which the cryo-extractor had been attached and [illegible] the lens were cut away Small pieces of the anterior structures (about [illegible] further fixed in freshly prepared fixative for 2 h postfixed in [illegible] OsO_4 [illegible] cacodylate buffer dehydrated in graded acetone and embedded in Epon 812 [illegible] of 1 µm were stained with toluidine blue examined and photographed in a [illegible] microscope Ultrafine sections were cut with diamond knife in a Reichert [illegible] U3 and stained with 1% uranyl acetate for 45 min and 1% lead citrate for 5 [illegible]

-ned in a Zeiss EM 9S 2 electron microscope at 60 kV or a JEOL 100 C at 60-80 kV The
s of negatives studied were magnified three times Magnifications used for illustration
ted in the legend

SEM the fixed postfixed and dehydrated whole lenses were critical point dried in a
on critical point drying apparatus E 3000 the acetone being replaced by liquid CO_2 and
ht through the critical point at about 1600 psi and 40 C The specimens were fixed on
stubs with colloidal silver and coated with 50 nm Au Pd in a Polaron E 5100 Series II
sputter Scanning was performed in a JEOL JSM 35 at 15 kV

subsequent TEM the lens was removed from the SEM stubs with a razor blade small
s of 1 mm³ of the anterior surface cut out and then placed in a propylene epon mixture
for 4 h in vacuum and for 2 h in pure epon before polymerization at 60 C for 48 h
ter processing as above

Results

ignificant difference was found between lenses fixed by the various fixatives or
ive concentrations

the following the most important similarities and differences are reported
een lenses with (immature and totally opaque lenses) and without ACSCO
nature cataractous lenses)

sule

showed no difference between the capsule of the various types

TEM examinations granular inclusions as described by Seland (1974 1978)
irred in both categories of lenses particularly in totally opaque lenses (Fig 1A
C) No quantification was made but no pronounced difference between
nature cataractous lenses with and without ACSCO as concerns capsular
usions was observed

EM revealed no difference between the surfaces of lenses with and without
SCO

helium

he light microscope cataractous lenses with and without ACSCO had as a rule
pronounced epithelial vacuoles They were located predominantly in the
... two-thirds of the epithelium (Fig 2A B) Here and there areas without
uoles were seen – even in totally opaque lenses In a few cases of total lens
city areas of epithelial atrophy with total cell loss occurred centrally

n TEM the vacuoles were identical in the two categories of cataractous lenses
l were seen as numerous large intercellular and a few intracellular vacuoles The
ercellular vacuoles contained small processes of cytoplasm possibly detached
m the wall (Fig 3A) and such material often merged with electron-dense coiled



Fig 1 A B C

A Cranular inclus o is n capsule and ep thel um 4 crisks) d = dense b
= vacuole Totalls opaque lens Lab N 515 78 TEM 3101 3 0

B M nc r granular nclusions n capsule of totall opa que lens arro 1





Fig 2 A B

ACSCO in immature cataract Vacuoles in the anterior part of the epithelium (e) The subepithelial cortex heavily changed with varying thickness of lens fibres and bladder cells of W (W) and vacuoles (V) c = capsule 1 µm section. Toluidine blue Lab No 744/78 (× 950)

Totally opaque lens Epithelial (e) and cortical (V) vacuoles globules (Gl) and subepithelial amorphous substance (arrow) 1 µm section Toluidine blue Lab No 658/78 (× 950)

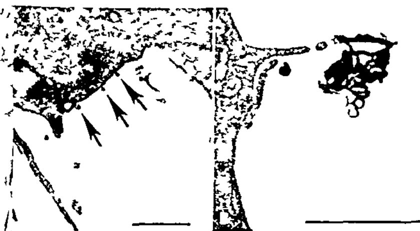


Fig 3 A B

Small cytoplasmic bodies possibly being detached from wall of epithelial intercellular vacuole (arrows) Immature cataract with ACSCO
Lab No 253/78 TEM 283A (× 14 400)

Coiled string like masses possibly derived from cytoplasmic process Wall of epithelial intercellular vacuole at left Immature cataract with ACSCO
Lab No 831/78 TEM 334 A (× 28 500)



Fig 4 A B

A Intraepithelial vesicles (ve) in immature cataract with ACSCO m = mitochondr
Lab No 744/78 TEM 324 (× 28 500)

B Intraepithelial vesicles (ve) and Golgi apparatus (G) beneath the nucleus (N). Defi
subepithelial fiber (arrow) Immature cataract with ACSCO Lab No 953/78 TEM
22 400)

string like masses (Fig 3B) Nuclei were often compressed by vacuole irregular shapes in both categories (Fig 11) Small vesicles or intracellular va were observed in both categories particularly at the cortical end of the cell, p in connexion with the Golgi apparatus (Figs 4A B 8) Mitochondria with cristae were seen in large quantities in all ACSCO lenses (Figs 4A 5C, 6), wh some lenses without ACSCO showed few mitochondria and in no case mitochondria than lenses with ACSCO

Dense bodies as described by Gorthy et al (1971) occurred in both sometimes near or on the epithelio-cortical borders (Figs 1A 5A, 8 19) E endocytotic vesicles were seen to open on the capsular as well as on the co aspect of the epithelial cell in both types (Fig 5D E) Endoplasmic reticulum to the nuclei as well as the Golgi apparatus also appeared identical in the categories of lenses



Fig 5 A B C D E

pithelial multivesicular body (mv) adjacent to flat cortical vesicle (ve) Totally opaque lens Lab No 688/78 TEM 393 (× 57 000)

ortical multivesicular body (mv) on cortico-epithelial border (m = mitochondrion) Totally opaque lens Lab No 688/78 TEM 323 (× 57 000)

ortical vesicle (ve) on cortico-epithelial border of totally opaque lens (m mitochondria) Lab No 897/78 TEM 341 (× 44 800)

xo endocytotic vesicles on the epithelio-capsular border (arrow) c = capsule Immature cataract without ACSCO Lab No 1128/77 TEM 239 (× 37 000)

ossible epithelial exo endocytotic vesicle on cortico-epithelial border (arrow) Immature cataract with ACSCO Lab No 744/78 TEM 394 (× 60 000) All scale bars 0 1 µm

rtex

ht microscopically the subepithelial cortex was regular and uniform in lenses thout ACSCO but heavily distorted in ACSCO lenses (Fig 2A B)

In the latter bladder cells of Wedl (Fig 2A) globules vacuoles and amorphous bstance of varying density were usual (Fig 2A B)

By TEM the most anterior cortical fibre of all cataractous lenses was thinner and metimes darker *than the deeper cortical fibres (Figs 4B 6 7) The subepithelial* res of ACSCO lenses were obviously of the deep (midzonal) type as described by uwabara (1975) and Kobayashi & Suzuki (1975) As illustrated in Fig 6 they are

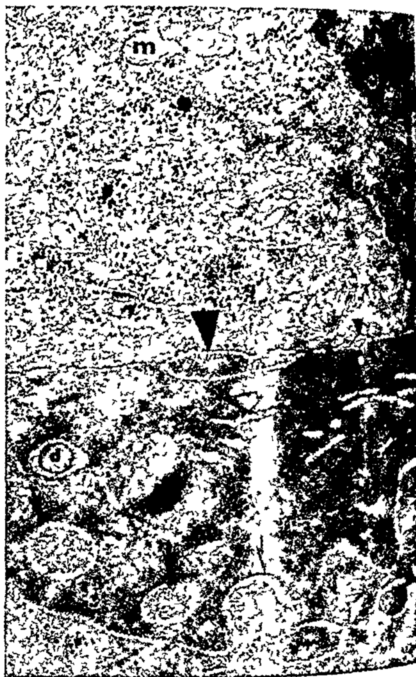
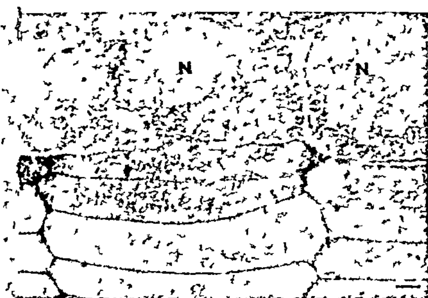


Fig 6

Interlocking processes (black arrows) circumscribed cytoplasmic material between epi… and cortex (arrow heads) and intrafibral clefts (open arrows) d = cortical dense bod… epithelial glycogen m = epithelial mitochondrion N = nucleus Immature catara…
ACSCO Lab No 744/78 TEM 324 (× 57 000) Scale bar 0 1 µm



F g

u e cataract w thout ACSCO show ng regular lens fibres F bres mmedia ely beneath the ep hel um are da k. N nucleus Lab No 1198 TEM 949 (× 5 00)

acterized by many interlocking processes as well as by their rregular shape In trast, the subep thelial cortical f bres of lenses without ACSCO had few rlock ng processes and a more regular shape (F g 7) In the intercellular space een ep thelial and cortical cells small bodies probably cons sting of cytoplasm sometimes observed in ACSCO lenses (Fig 6)

CSCO lenses displayed a variety of additional degenerative changes in the p thelial cortex Intraf bral clefts (F gs 4B 6) l quefaction of lens f bres (F g mall and large globules (F gs 8 9) multivesicular bodies (F g 5B) dense bodies 6) and ves cles often located adjacent to or on the ep thelio-cortical borders 5 A C) Here and there an ep thelial multives cular body was adjacent to a formed cortical ves cle or multives cular body on the ep thel o-cortical borders 5A) A few exo- or endocytotic ves cles opened on the ep thelium (F g 10) ilar degenerative changes as described above were observed sporadically in the anterior cortical f bre of lenses without ACSCO In some ACSCO lenses reme th nning of lens f bres and lam nated arrangement of these structures were n in the subep thelial cortex, probably densely packed plasma membranes from apsed f bres as described by Dilley et al 19 6 (F g 11)

n both categories of lenses desmosome like junctional complexes were seen on ep thelio-cortical borders (Fig 12)



F g 8

ACSCO n immature cataract. Liquefied lens fibre with globules (Gl) and partially fibres (arrows) d ep thelial dense bodies V = epithelial acuole e epi ela
Lab No 1214 77 TEM 245 (× 9 900)

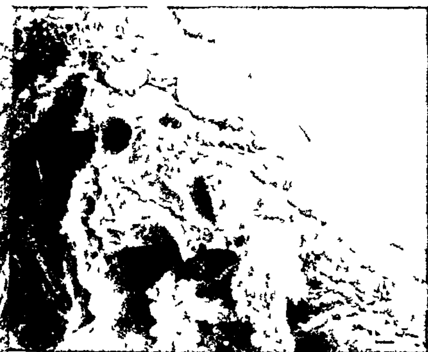


Fig 9

picture of globules in cortex of immature cataract with ACSCO Lab No 1224/77 SEM 248 (× 3 900)

Discussion

find it probable that the histopathological basis of ACSCO is the subepithelial cal changes clearly seen in ACSCO lenses at the light microscopical level The elial vacuoles are probably not of great importance for the biomicroscopical arance of ACSCO since they were more often than not of the same size and ber in lenses with and without ACSCO Additional epithelial and all capsular ges were seen only at the electron microscopic level Consequently we doubt these changes are visible at the biomicroscopic level However an association een increased light scattering due to these ultrastructurally visible phenomena the biomicroscopical appearance of ACSCO cannot be totally excluded

he finding that the subepithelial fibres of ACSCO lenses were of the deep cal type calls for and explanation We suggest two possibilities a) break-down uperficial cortex fibres and removal of the decomposed material through helium and capsule into the aqueous or b) formation of degenerated lens es possibly from the equatorial cells We support the first – for the following sons



Fig 10

Cortical exo endocytotic vesicle on the cortico-epithelial border (arrow) Immature … with ACSCO Lab No 313 77 TEM 199 (× 15 000)

Fig 11

Laminated pattern of possibly collapsed lens fibres (asterisks) in a totally opaque … Nucleus distorted by vacuole N = nucleus Lab No 153/78 TEM 327 (× 10 000)

1) Intra and extracellular lysosomal hydrolases have been demonstrated … epithelium and the anterior cortex and seen as responsible for the break-down … epithelium and cortex in rat (Gorthy 1978) and human (Francois & … Troncoso 1978) cataractous lenses

2) Break down of subepithelial lens fibres and epithelial cell tissue obviously … place in ACSCO as indicated by the occurrence of large intercellular spaces …



Fig 12

mosome like junctions between epithelium and cortex (arrows) and between epithelial (double arrow) d = epithelial dense body Immature cataract w thout ACSCO Lab No 1198 77 TEM 939 (× 35 600)

vacuoles with cytoplasm being detached from the wall as well as by the [illegible] disintegration liquefaction and collapse of subepithelial cortex fibres.

3) The system described by Gorthy et al (1971) and Unakar et al [illegible] transporting decomposed lens fibre material via the epithelium was [illegible] epithelium and cortex This system comprises multivesicular bodies, dense [illegible] and vesicles

4) The transport vesicles and multivesicular bodies in ACSCO lenses were [illegible] located adjacent to or on the epithelio-cortical borders. Some vesicles and m[illegible] cular bodies were observed opposite each other on either side of the borders [illegible] an exchange of material from cortex to epithelium or vice versa appears p[illegible]

5) *The numerous mitochondria in ACSCO lenses indicate the possibility of [illegible] mitochondrial (oxidative) metabolism in ACSCO lens epithelium to provide [illegible] energy necessary for the transport.*

6) ACSCO as well as posterior subcapsular cataract is associated with lens [illegible] *to a degree that cannot be accounted for solely on the basis of cessation of lens growth (Bruun Laursen & Fledelius 1979)*

7) ACSCO in immature cataractous lenses is associated with a slight but [illegible] significant decrease *in whole lens water percentage (Klauber & Bruun L[illegible] 1977) This is to be expected if cortex material which is richer in water th[illegible] nucleus (Fisher 1977 Rink 1978) leaked out of the lens and cons[illegible] decreasing proportion of the lens substance*

8) In the aqueous of human eyes with *senile cortical cataract, the α and [illegible] crystallins have been found to occur in increasing concentrations as compare[illegible] non cataractous eyes (Sandberg & Closs 1979)*

Having regard to the present results we assume the histopathological ba[illegible] biomicroscopical opacity so far called ACSCO *to consist mainly of subep[illegible]* degenerative cortical changes We therefore at present *find the term* (anterior subcapsular opacity) more appropriate than ACSCO although [illegible] microscopically visible capsular inclusions were pronounced *in the late p[illegible]* ASCO lenses viz *in totally opaque lenses* We had no *impression of a qua[illegible]* difference *as for capsular inclusions* in immature *cataractous lenses w[illegible]* without ASCO but on the other hand we cannot rule out a *gradual inc[illegible]* capsular inclusions as ASCO propagates – particularly since we consider to[illegible] opacity the final stage of ASCO development

Hypothetically the decomposition of the superficial cortex fibres may be [illegible] influx of lysosomal hydrolase activators or outflow of inactivators fr[illegible] through the lens membranes Capsular inclusions epithelial vacuolisa[illegible] disintegrating subepithelial cortex fibres may be phenomena associat[illegible] increasing permeability of the functional lens membranes The decompo[illegible] material may pass via epithelium and lens capsule into the aqueous humour

Acknowledgments

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References

aursen A (1976) Concentrations of some ribonucleotides L lactate and pyruvate in n senile cataractous lenses with special reference to anterior capsular subcapsular y *Acta ophthal (Kbh) 54* 677–699

Laursen A & Fledelius H (1979) Variations of lens thickness in relation to croscopic types of human senile cataract *Acta ophthal (Kbh) 57* 1–13

J Bron A J & Habgood J O (19 6) Anterior polar and posterior subcapsular ct in a patient with retinitis pigmentosa a light microscopic and ultrastructural study *Eye R s 22* 155–167

R F (1977) Changes in the permeability of the lens capsule in senile cataract *Trans al Soc U K 97* 100–103

s J & Victoria Troncoso V (1978) Histology of the epithelium of the normal and actous lens *Ophthalmol gica 177* 168–174

W C Snavely M R & Berrong N D (1971) Some aspects of transport and digestion e lens of the normal young adult rat *Exp Eye Res 12* 112–119

W C (1978) Cataracts in the aging rat lens Morphology and acid phosphatase chemistry of incipient forms. *Exp Eye Res 27* 301–392

(1905) Pathologie und Therapie des Linsensystems In Saemisch T ed *Handbuch esamten Augenheilkunde 6 Band* pp 46–47 Verlag von Wilhelm Engelmann Leipzig

r A & Bruun Laursen A (1977) Relative contents of sodium potassium water and dry er in human senile cataractous lenses in relation to anterior capsular/subcapsular ity *Acta ophthal (Kbh) 55* 789–799

ashi Y & Suzuki T (1975) *The aging lens ultrastructural changes in cataract In* ows J G ed Cataract and Abnormalities of the Lens pp 313–343 Grune & Stratton New York San Francisco London

bara T (1975) The maturation of the lens cell a morphologic study *Exp Eye Re 20* –443

I (1978) The water content in bovine lenses during aging *Inte d pl Topics Ge nt 12* –9 7

erg H O & Closs O (1979) The alpha and gamma crystallin content in aqueous nour of eyes with clear lenses and with cataracts *Exp Eye Res 28* 601–610

J H (1974) Ultrastructural changes in the normal human lens capsule from birth to age *A ta ophthal (Kbh.) 52* 688–706

J H (1978) The ultrastructure of the human lens capsule I Cataractous lenses from s with *simple glaucoma A transmission electron microscopic study Acta ophthal (Kbh)* 715–799

J H (1978) The ultrastructure of the human lens capsule II Cataracta complicata. A nsmission electron microscopic study *Acta ophthal. (Kbh.) 56* 723–734

ar N J Weinsieder A & Reddan J R (1977) *Ultrastructural changes associated with* induction and reversal of chemically induced cataract *Ophthal Res 9* 296–307

A (1914) Klinischer und anatomischer Beitrag zur Kenntnis der Cataracta senilis ku lenbildungen *Albrecht v G aefes A ch Ophthal. 88* 362–365

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HUMAN SENILE CATARACT AND Na K ATPase ACTIVITY THE ANTERIOR LENS STRUCTURES

with special reference to anterior capsular/subcapsular opa

BY

A BRUUN LAURSEN A KLAUBER and O A JENSEN

Location and *in vitro* determination of Na K ATPase activity in the anterior structures of individual human lenses with senile cataract are reported with special reference to anterior capsular subcapsular opacity (ACSCO)

Histochemically ATPase reaction products were found exclusively in the epithelium Even totally opaque lenses showed strong positive reaction. Biochemically increasing ratios of Na^{+}/K^{+} concentrations in the assay medium resulted in an increase in enzyme activity to a limited degree whereafter the activity remained stable

We cannot decide whether the Na K ATPase activity of the anterior lens structures is unchanged in relation to ACSCO as indicated by our figures. For there are methodological problems although our analytical error expressed as the variation coefficient for slaughterhouse pig lenses seems to be one of the lowest so far reported in the literature on interindividual non pooled materia

Key words sodium potassium ATPase – epithelium of the lens cataract human senile – biomicroscopy – histochemistry – biochemistry

Na K ATPase (sodium potassium activated adenosine 5 triphosphatase) is cal with the active cation pump which transports Na^{+} out of and K^{+} in (Skou 1965) and the lens (Bonting 1965) This cation pump is active at anterior lens surface and is located chiefly in the epithelium (Harris & Becker Kinsey & Reddy 1965) The pump is particularly active in the anterior central disc (Becker & Cotlier 1962)

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a K ATPase is specifically inhibited by ouabain (Skou 1960) By means of bitor the enzyme has been located *biochemically* primarily in lens epithelium g 1965 Neville et al 1978) and low activities have been found in cortex and (Bonting 1965 Neville et al 1978) *Histochemically* Palva & Palkama (1974 using the Wachstein Meisel method the specificity of which has been under on (Firth 1978) found rat lens Na K ATP'ase activity between adjacent al cells and on some elongating equatorial fibres as also did Unakar & Tsui using the method of Ernst In addition these latter authors found Na K e activity in the epithelial membrane in juxtaposition with the cortex as well e membranes of the anterior polar lens fibres

aim of the present study was to examine a possible correlation between the ATPase activity in the anterior lens structures and the extent of the roscopically visible anterior capsular/subcapsular opacity (AC SCO) (Bruun n 1976) previously found to be an indicator of increasing $C_N + C_K$+ ratio in is water (Klauber & Bruun Laursen 1977) The study was carried out by a) gating the histochemical location of ATP'ase reaction products in the or part of the lens b) biochemical analysis of the enzyme activity in the or lens tissue and c) examining the influence of changes in the $C_N + /C_K$+ on the activity of the enzyme system

Material

udy comprised 68 human lenses with uncomplicated senile cataracts as well as 94 lenses 12 pigs (slaughterhouse material) *Histochemically* 34 lenses were studied The material ted of 16 specimens of anterior lens structures (capsule and adjacent lens tissue) from ts aged 62 89 years Eight of these lenses had 0-10% ACSCO and six had 100% O (Two lenses were lost during incubation) Further the anterior structures of 18 lenses from 61 87 years-old patients were examined

biochemical part comprised the remaining 34 lenses from patients ranging in age from 90 years Enzyme activity was determined in the anterior tissues of 30 and in the rior structures of 4 cataractous lenses Cataractous lenses were selected and classified as ibed by Bruun Laursen (1976) However noradrenaline and phenylephrine were not ed and the patients were not fasted

e following chemicals of analytical grade were used in the analyses disod um hydrogen phate (Merck) EGTA (ethylene glycol bis (β-aminoethyl-ether N N' tetraacetic acid) k ATP-disodium (Boehringer Mannheim) bovine albumin (Sigma) oubain (Sigma) gelatin (Difco-laboratories) In the following water is aqua redestillata sterilisata sted to pH 7 5 8 5 by 1 drop of 0 1 N NaOH to 10 ml H O All other reagents used were alytical grade Na^+ K^+ and Mg^{2+} were added as chlorides

he solutions used in the *histochemical* exam nations were according to Palva & Palkama 4) except for a 4% solution of formaldehyde in an 0 2 M tris-HCl buffer pH = 7 2 being for prefixation The following solutions were used in the *biochemical* investigations 1)

um reagent 4 4% of ammonium heptamolybdate in 3 N sulphuric acid 2) 25% of n water 3) imidazole HCl buffer 50 mM pH = 7 5 For the composition of blank and dia various chemicals were added to the homogenates (cf Methods) 4) phosphate n hydrogen phosphate (various concentrations) in a 1 2% solution of albumin in) TCA reagent 7% of ferroammonium sulphate in 25% of trichloroacetic acid

Methods

hemical demonstration of ATP ase activity

iately after cataract extraction the lens capsule was opened by a cross section in the or surface The posterior cortex and nucleus were removed before incubation lenses were also incubated Incubation was carried out by means of the Wachstein method modified by Palva & Palkama (1974) except for the above mentioned tion for 10 min The incubated lens material or lens was transferred to Ames O C T und and cut into 5 μm sections in an American Optical cryostat at –30°C The sections amined unmounted or mounted with glycerin They were studied and photographed eitz orthomat microscope using Agfachrome 50 L professional film Copies were ied six times The peripheral site of the cryo-application was excluded from copy

emical procedure

ryo-extraction the site of the cryo-application was marked The lens was placed on ice the anterior surface upwards and immediately transported to the laboratory where it nsed in imidazole buffer One drop of gelatin (prepared the same day) was applied to nterior lens surface and equator to reinforce these sites When the gelatin was iently hard a 7 mm cylinder (corresponding to 38 5 mm^2) of the anterior structures was ined and sliced under the dissection microscope The specimen (weight 25-53 mg) – ting of hardened gelatin lens capsule epithelium and anterior cortex – had a thickness 1 mm It was ground for 3 min in 500 μl of water in a Potter Elvehjem homogenizer on ath and incubation followed – in a modification after Skou (1957 1965) The genate was transferred to a phial and stored at –80 C until used After thawing and g 50 μl aliquots were incubated for exactly 60 min at 37 C in disposable plastic tubes with 30 μl imidazole buffer and 50 μl enriched medium Blank tubes contained in in addition The final concentrations in the assay and blank media were imidazole 30 ATP 3 mM (disodium salt the sodium being included in the total C_{Na} + of the medium 136 mM K^+ 90 mM Mg^{++} 4 mM In addition the blank tubes contained 1 mM ouabain

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Fig 1

ATPase *reaction products in the epithelium of human senile immature cataractous lens* out ACSCO The black reaction products are seen in the epithelium exclusively hstein Meisel Method Lab no 332 78 (× 400) B Location of ATPase reaction ducts at cell borders of epithelial cells in an immature senile cataractous whole-lens out ACSCO Wachstein Meisel Method Lab no 75 8 (× 540) C Epithelial cells from lly opaque lens with *abundant ATPase reaction products* particularly at cell borders Tangential section Wachstein Meisel Method Lab no 319 8 (× 400)

The prote n concentrat on was approx mately 0 3 0 6% (calcula ed from dur protein percentage – Klauber & Bruun Laursen 1977) Furthermo e in akrn of the Na K ATP ase in the anterior structures of each ndi dual lens was dete following C_{Na}+ C_K+ rat os n the assay med um 6 150 36 190 81/ meq l

The reaction was halted after 60 m n by add t on of 995 µl TCA. The coloured with ammon um reagent (volumes 10 1) and incuba ed a room tempera min Absorbance at 660 nm of samples and blanks were reco ded in a spectrophotometer The concentrations of norgan c phospha e split off from calculated from a standard curve and gi en as nmol P mm anterior lens Standard curves were prepared every 2 3 weeks The equat ons of the standa calculated by means of regress on analys s The slope varied be ween 0 41 a d0 y intercepts never d ffered s gn ficantly from 0 Da ly pho pha e standards wer The median difference between 30 dupl cated determ nations of cataractous ATP ase activity at the C_{Na} +/C_K+ rat o of 136 20 was 0 4 nmol P mm² and the 0 2 8 nmol P/mm² (cf F g 2)

The p g eyes were stored on ice the corneas and irides cut away and the lenses a drop of gelatin The lenses were treph ned w th a 7 mm treph ne 9 h post me we gh ng 48 177 mg were homogen sed n 1000 µl of wa er and further p described above (C_{Na}+/C_K+ ratio 136 20 meq l)

The correlation between correspond ng values of enzyme act y and the esu was calculated by means of the Spearman rank correlation analysis Compariso groups were carried out by means of the Mann Wh tney test

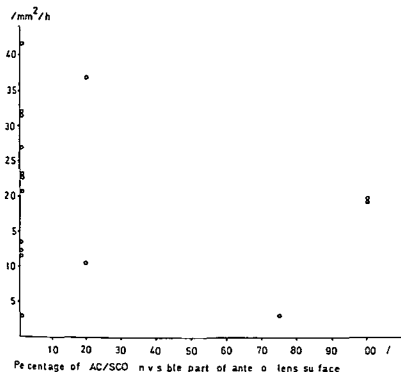
Results

H stochem cal locat on of ATP ase react on products n the an erior ens struc

The dark brown reaction products of the method used occurred amounts exclusively in the ep thelium (Figs 1A and B) Ep thelium opaque lenses showed as a rule strong pos tive reactions (F g 1 C) T products were located as tiny granules in the cytoplasm but particul borders (Figs 1 B and C) The reaction could not be inh b ted by means mM of ouabain The precipitate therefore probably included mo e tha sensitive ATP ase reaction product (such as Mg^{2+} and Ca^{2+} ATPa products) The possible occurrence of reaction products n the lens nucl posterior cortex was not examined in this study

Specif c b ochem cal Na K ATP ase activity determ nat ons

No significant change in the enzyme activity was found as ACSCO Totally opaque lenses revealed activities comparable to those of sl ght lenses without ACSCO (Fig 2) which ind cates that the Na K ATPas independent of cataract type and density The median Na K ATPase at 30 cataractous lens samples at the C_{Na} +/C_K+ ratio of 136 20 was 18 1 n anterior lens structures/h and the range was 2 4-42 6 In comparison of the 24 pig lenses was 61 nmol P/mm² h the range be ng 33-95 (S



F g 2

ATPase acu n he an enor lens s ructu es as a function of he ex en of ACSCO ı alue rep esen s he mean of two de erm na ons The enz me acu s gı en as an c pho phate (P) relea ed per mm and h $C_\backslash + C_K$ was 136 20 meq l \ 30 $P >$)01 o mmature ca ara ous lenses • totall opaque lenses

ant value was excluded) The range as larger for the p g lenses when \a K ase act tv was expressed on wet we ght bas s (0 86-5 06 μmol P g/h med an 91) \o s gn f cant d fference was found between ntra and nternd vidual t on of lens pairs from 12 p gs

ı K ATPase actı t es n 7 mm d scs of posterior structures of 4 human actous lenses varied between 0 and 9 2 nmol mm² h

ence of nc eas ng $C_{Na}+/C_K+$ rat o of the med um on the act v ty of Na K ATP ase n n eno lens structu es

eas ng C + C_K+ ra os from 6 150 to the le el of 81 75 meq l resulted n ıf cant ($P < 0$ 01) ncrease n \a K ATPase act ty (F g 3) Add uonal ncrease e sod um concentrat on and reduction n the potass um concentration d d not her ncrease the med an \a K ATP ase act v ty D fferences n actı ty between

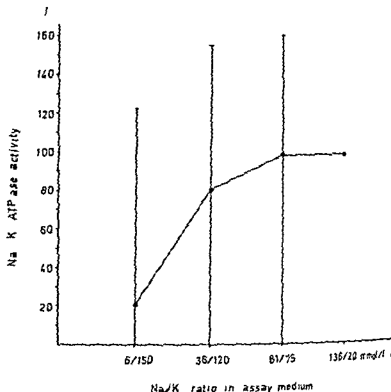


Fig 3

Na K ATP'ase activity in the anterior lens structures as a function of the C + C the assay medium The activity found at the ratio of 136 20 was given the value point shows the median value – the bars represent the ranges. The 0-values corre the C_{Na} + C_K+ ratios of 36/120 and 81/75 were derived from a lens specimen with activity of 2 4 nmol P per mm and h at the ratio of 136 20 N – 2

groups of lenses with and without ACSCO was insignificant at all C_{Na}+ C_K examined

Discussion

In the present study the Na K ATPase activity was expressed in rela constant biomicroscopically visible area of the anterior lens surface following reasons 1) Histochemical ATP ase reaction products of the an structures were found to be located in the epithelium only 2) In addi lenses the Na K ATP'ase activity range was smaller when expressed anterior lens tissue than on wet weight basis 3) Furthermore the measured in the posterior lens structures of cataractous lenses were

o not consider it expedient to express lens Na K ATPase activity in relation e lens protein firstly because it appears to be inexpedient to express the activity in relation to structures where the enzyme does not seem to lodge s cortex) and secondly because protein percentage and solubility changes cataract development (Mach 1963 Maraini & Mangili 1973) 5) The central r lens structures were chosen for Na K ATPase activity assay because cation rt appears to be most active here (Becker & Cotlier 1962)

$C_{Na}+/C_K+$ ratio of ACSCO lenses increases with increasing extent of) (Klauber & Bruun Laursen 1977) As indicated by Duncan (1973) such a may be due to 1) decreasing lenticular Na K ATPase activity or asing permeability of the ion restricting lens membranes In the present t material we have tried to investigate the possibility of decreasing Na K se activity in relation to ACSCO However our examinations as well as those er authors investigating the Na K ATPase activity of cataractous lenses burg 1973 Gupta & Harley 1975 Nordmann & Klethi 1976) show that Na K se activities vary within large ranges This may be due to break-down of ial cells as indicated electron microscopically by the occurrence of large llular vacuoles in the epithelium of cataractous lenses with and without O (Jensen & Bruun Laursen – to be published) However our examinations K ATPase activities in pairs of pig lenses indicate methodological sources of

Table I

dividual Na K ATPase activity ranges in tissues from normal animals Coefficients of ariation for data from the literature as well as for our pig lens material (N = 24)

Authors	Year	Animal	Coefficient of variation	Na-K ATPase activity expressed per
Kinoshita	1971	mouse	ca 0 39-1 07	whole lens
iann & Klethi	1976	calf	0 24	g insoluble lens protein
iann & Klethi	1976	cow	0 86	g insoluble lens protein
ey et al	1975	rat	0 24-0 29	g protein of ileal epithelium
ey et al	1975	rat	0 12	g protein of jejunal epithelium
Davis & Charney lated procedure)	1977	rat	0 10-0 14	g intestinal epithelium
: et al	1978	rabbit	0 36	lens capsule + epithelium
ton et al	1979	rabbit	0 74	g anterior lens tissue
ann et al	1979	calf	ca 0 46	mg insoluble lens protein
i Laursen er & Jensen	1980	pig	0 25	mm anterior lens tissue

error the intraindividual variation not differing significantly from the interindividual variation Nevertheless our coefficient of variation for the pig lenses appears to be one of the lowest so far reported in the literature interindividual variation in non pooled materials of clear lenses (Table) do not feel able to decide whether the distribution of Na K ATPase in relation to ACSCO (Fig 2) is due to validity of the 0-hypothesis or to logical errors Even though our median activities for cataractous lenses ACSCO and with 100% ACSCO were 22 6 and 19 8 nmol P mm h re i e almost identical The methodological source of error may very well be with the formation of tiny vacuoles during homogenisation. Our determinations on identical lens homogenates showed very small variations (Methods) Determinations on pooled homogenates also showed much variations than the intraindividual variations Unfortunately attempts to problem of possible vacuolisation by using detergents in the procedure genisation were futile since the ultracentrifugate could not be eff suspended

According to Fig 3 increasing $C_{Na}+/C_K+$ ratio as seen in ACSCO lenses associated with increasing Na K ATPase activity up to a certain ACSCO lenses the Na^+ stimulated pump activity may soon reach a maximum is consistent with kinetic the finding of Kinsey & Hightower (1978). Apart important detail it is our belief that no precise information on Na activity in relation to senile cataract is available at present and will not be methods have been developed for liberating the membrane bound Na from the cell walls of the cataractous lenses

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References

Becker B & Cotlier E (1962) Distribution of rubidium 86 accumulated in the Invest Ophthal 1 642–645

Bonting S L (1965) Na K activated adenosinetriphosphatase and active cation the lens Invest Ophthal 4 723–738

Bruun Laursen A (1976) Concentrations of some ribonucleotides L lactate and human senile cataractous lenses with special reference to anterior capsular opacity Acta ophthal (Kbh) 54 677–692

y A \ Kinse) A D Myers L G anella R A & Gots R E (1975) \a+ K+ acti a ed os ne triphosphatase and n estinal electrolyte transport J Cl n I v t 56 653 660
D P Davis J I & Charney A \ (1977) An impro ed automa ed determ nat on of K+ acti ated adenos ne tr phosphatase Anal B ochem 9 438 446
n G (19 3) Role of membranes in controll ng on and water mo ements n the lens In Foundation Sympos um 19 (new series) The human lens n relation to cataract pp 116 Else ier Excerpta Med ca North Holland Amsterdam London New York
J A (19 8) Cytochem cal approaches to the local zation of specif c adenos ne triphos tases Histochem J 10 253 °69
burg D (19°3) Enzyme activity patterns n clear human lenses and n d fferent types of nan senile cataract In C ba Foundation Sympo um 19 (new series) The human lens elat on to cataract pp 117 133 Else er Excerpta Med ca North Holland Amster London New York
J D & Ha ley J D (19 5) Decreased adenos ne triphosphatase acti ty n human le cataractous lenses Exp Eye Res 20 °07 °09
on P M Delamere N A & Paterson C A (19 9) In e t Opt hal V is Sci 18 434 436
J E & Becker B (1965) Cation transport of the lens I e t Ophthal 4 09 °°
S & Kinosh ta J H (1971) Mechanism of development of hered tary cataract n m ce st Ophthal 10 504 512
V E & Reddy D V N (1965) Stud es on the crystall ne lens XI The relat e role of ep thel um and capsule n transport In est Ophthal 4 104 116
V E & H ghtower K R (19 8) Stud es on the crystall ne lens XXVI Kinet c stud es wing saturation of the sod um pump In e t ophthal I 186 189
er V & Bruun Laursen A (19 7) Relative contents of sod um potass um water and ma er n human sen le cataractous lenses n relation to an erior capsular subcapsular ity A ta phthal (Kbh) 55 89 99
H (1963) Untersuchungen von Linsene we ss und M kroelektrophorese von wasser chem E we ss m Altersstar Kl Mbl A g he lk 143 689 710
n G & Mangl R (1973) D fferences n proteins and n the water balance of the lens n clear and cortical types of senile cataract In C ba Foundation S mpos um 19 (new es) The human lens n relat on to cataract pp 9 9 Else ier Excerpta Med ca rth Holland Amsterdam London New York
an C I M ller D & T jerina M L (19 9) In tro product on of s ero d cataract in ine lens Part II Measurement of sodium potassium adeno ne triphosphatase act v ty a phthal (Kbh) 5 1107 1116
le M C Paterson C A & Ham lton P M (19 8) Ev dence for two sod um pumps n the stall ne lens of the rabb t eye Exp E e Re 2 637 648
mann J & Kle hi J (19 6) L act e \a K ATP as que dans le cristall n normal il sant et dans la cataracte sen le A h Ophtal P ris 6 5°3 5°8
M & Palkama A (19 4) H stochem cally demonstrable sod um potass um act a ed enos ne triphosphtase (Na K ATPase) act v ty n the rat lens Exp E e Re 19 117 123
M & Palkama A (19 6) Electronm croscop cal h stochemical and b ochem cal f nd ngs the Na K ATPase activity n the ep thel um of the rat lens E p Ey Re 22 °°9 °36
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J C (1960) Further n est gat ons on a Mg + + Na+ acti ated adenos ne triphospha e poss bly related to the acti e l nked transport of Na+ + K+ across the nerve mbrane Bioch m Biophy A ta 42 6 23

error the intraindividual variation not differing significantly from the interindividual variation Nevertheless our coefficient of variation for pig lenses appears to be one of the lowest so far reported in the literature interindividual variation in non pooled materials of clear lenses (Table 1) We do not feel able to decide whether the distribution of Na K ATPase activity in relation to ACSCO (Fig 2) is due to validity of the 0-hypothesis or to methodological errors Even though our median activities for cataractous lenses with ACSCO and with 100% ACSCO were 22 6 and 19 8 nmol P mm h respectively i e almost identical The methodological source of error may very well be associated with the formation of tiny vacuoles during homogenisation Our duplicate determinations on identical lens homogenates showed very small variations (see Methods) Determinations on pooled homogenates also showed much smaller variations than the intraindividual variations Unfortunately attempts at solving the problem of possible vacuolisation by using detergents in the procedure of homogenisation were futile since the ultracentrifugate could not be easily suspended

According to Fig 3 increasing $C_{Na}+/C_K+$ ratio as seen in ACSCO lenses is associated with increasing Na K ATPase activity up to a certain limit In ACSCO lenses the Na+ stimulated pump activity may soon reach a maximum This is consistent with kinetic the finding of Kinsey & Hightower (1978) Apart from this important detail it is our belief that no precise information on Na K ATPase activity in relation to senile cataract is available at present and will not be until methods have been developed for liberating the membrane bound Na K ATPase from the cell walls of the cataractous lenses

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References

Becker B & Cotlier E (1962) Distribution of rubidium 86 accumulated in the rabbit *Invest Ophthal 1* 642–645

Bonting S L (1965) Na K activated adenosinetriphosphatase and active cation transport in the lens *Invest Ophthal 4* 723–738

Bruun Laursen A (1976) Concentrations of some ribonucleotides L lactate and pyruvate in human senile cataractous lenses with special reference to anterior capsular opacity *Acta ophthal (Kbh) 54* 677–692

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NEW VISUAL ACUITY TEST FOR PRE-SCHOOL CHILDREN

BY

LEA HYVÄRINEN[1] RISTO NÄSÄNEN and PENTTI LAURINEN[2]

A new test chart was developed for the measurement of visual acuity of pre school children The symbols of the test are circle square apple and house These were so designed that each symbol measures visual acuity similarly This feature of the test was verified experimentally The visual acuity values measured by the individual symbols correlated highly with the visual acuity values measured with the whole test (0 82-0 86) The correlation between the visual acuity values measured repeatedly the reliability of the new test was found to be 0 94 for adult subjects The new visual acuity test thus fulfils the statistical criteria of a good visual acuity test Because both children and nurses seem to like the new test it may be useful in the assessment of visual acuity in pre school children

Key words vision tests – pre-school screening of visual acuity – line acuity tests

f a dozen different tests are used for testing the visual acuity of pre-school dren In two of them Sheridan-Gardiner and Fooks tests the child has copies of symbols in front of him and points to the symbol he thinks is shown at the chart s a single symbol In the Sjøgren test and Snellen E test one measures both visual ity and left right comprehension In picture charts the different figures asure visual acuity heterogeneously and the test requires ability to name some ely seen objects (Sheridan 1963) These charts work rather well in practice vever and therefore we undertook a test construction on this basis

A new visual acuity chart was developed by one of us (L H) for the measurement isual acuity of 3-5 years old children The chart was designed to allow the child espond either by pointing or by naming and the individual symbols were chosen hat their naming would be easy We present here a statistical analysis of the new t

eived October 22 1979

Test symbols

Square and ball and their derivate apple and house were chosen to [illegible] symbols The symbols were drawn in several slightly different forms until [illegible] blurred equally i e when seen with positive overcorrection or diffusing [illegible] became similarly blurred and were eventually seen as a diffuse ring in [illegible] cross appears in the centre

The reliability and validity of the new test and its item analysis

The symbols were studied by using seventeen 20 35 years old adults [illegible] Visual acuity was measured with a prototype of the new test chart and the [illegible] test chart at 6 m twice binocularly and monocularly with both eyes [illegible] candles/m²

Table I
Correlations between the new test and its individual test items

	Ball	Apple	Square	House
Whole test	0 86	0 82	0 86	0 84

Table I shows the correlations between the different test symbols [illegible] monocular measurements pooled (N = 34) The visual acuity values measured [illegible] each symbol have a high correlation with the visual acuity values measured [illegible] whole test (0 82 0 86) The symbols thus measure visual acuity similarly [illegible] structure of the test symbols fulfils the criteria of a good visual acuity test.

The reliability of the new test (correlation between repeated tests) was 0 9[illegible] corresponding reliability of the Snellen E test was 0 96 Both tests when repea[illegible] thus give the same visual acuity values

The relationship between the size of E symbol and the new symbols

This relationship was studied twice In the earlier phase of this work we used [illegible] subjects and found that the new test symbols have to be 1 5 times larger than [illegible] symbol in order to give same visual acuity (relationship 1 5 ± 0 05 [illegible] Following the introduction of the visual acuity chart, several colleagues rep[illegible] that the visual acuity values measured with the new chart were higher than [illegible] measured with the E chart Therefore the correlation was studied a second time

Thirty adult persons (20 35 years) were subjects Fig 1 shows the symbol [illegible] used The charts were shown at several different distances and the distance at [illegible] 25% of 100 answers were wrong was recorded

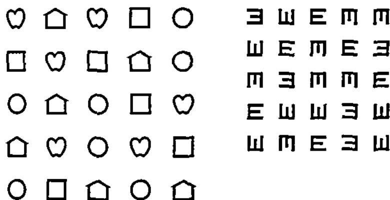


Fig 1

xamples of the E symbol chart and the new symbol chart used in comparing the size

e threshold tasks in these two tests are different when the E symbol is blurred e point of being barely perceptible it is seen as a dim C and the direction of E ol can be guessed by estimating which side of the symbol is lighter The new ols when blurred are recognized by the number of corners pointing either or into the dim ring *a visual task quite different from the recognition of the E* ol

e relationship between the size of the new symbols and the E symbol was now d to be 1 63 ± 0 18 Thus the symbols of the new chart are not too large they d be a fraction larger The lower visual acuity values of the children when using E test reflect the additional tasks involved (left right comprehension motor culues) unrelated to visual perception per se

new test chart

new chart resembles the Snellen E chart except that it was prepared for testing m. If used at 6 m the visual acuity values have to be multiplied by 2 The 3 m nce was chosen because the chart is meant for screening of visual acuity in th centres nursery schools and during home visits and there 3 m is a more tical distance than 5 or 6 m it also makes communication with the child easier he uppermost line 0 1 contains three symbols and thus functions better as a line than the regular E chart having only one 0 1 symbol (Bailey & Lovie 1976 wman 1975 Tommila 1972) The distance between the rows is equal to the ght of the symbols in the smaller row and the distance between the symbols is al to the width of the symbol (see Fig 2)

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PSEUDO EXFOLIATION MATERIAL

Electron Microscopy after the Application of Lanthanum as Tracer Particles and Ionic Stain

BY

MARTIN DAVANGER

Lenses with pseudo-exfoliation (PE) were suspended in a solution of lanthanum which was present partly in ionic form partly as electron-dense tracer particles in colloidal solution dependent on pH and on the concentration of lanthanum. By electron microscopy the tracer particles were found in a narrow zone along the surface of the PE excrescences Only a few of the smallest particles had penetrated into their most superficial layer In the specimens treated with ionic lanthanum the effect was an electron dense staining of the PE material within a 1 2 μm thick superficial layer The PE fibrils as well as parts of the interfibrillar spaces were stained These results indicate the presence of proteoglycans and confirm the concept of an interfibrillar matrix which excludes other macromolecules and particles from penetrating into the material

Key words pseudo exfoliation – amyloid – lanthanum – tracer particles

From a biochemical point of view the pseudo-exfoliation (PE) material is considered to consist of proteoglycosaminoglycans (proteoglycans acid mucopolysaccharides Morphologically the characteristic element is the PE fibril which can be seen by transmission and by scanning electron microscopy

The PE fibrils seem to be randomly distributed in three dimensions They are closely packed neighbouring fibrils are separated by a certain distance The space between the fibrils appears empty both by transmission and by scanning electron microscopy when the specimens are prepared by conventional methods H ever by the application of tracer molecules and also by special staining methods it has been shown that the interfibrillar spaces are filled with a ground substance The

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has the remarkable property that tracer particles are totally or partially
-d from the PE material (Davanger & Pedersen 1975 Davanger 1977 1978)
e present study lanthanum has been used in the preparation of PE material
-tron microscopy Two different properties of lanthanum have been used

gradually increasing pH of a solution of lanthanum nitrate colloidal particles
hanum hydroxide are formed These particles are electron-dense and they
= used as tracer particles in electron microscopical work (Revel & Karnowsky
The treatment of the PE material with lanthanum applied as a tracer may
-ore supplement earlier experiments in which other tracer substances have
ised

addition to the use as a colloidal tracer lanthanum has been used also in ionic
as an electron microscopical stain which binds to certain tissue components in
y with staining with other heavy metals (Schatzki et al 1975) Although the
ig mechanism is not well known it is assumed that ionic lanthanum has
y to proteoglycans acid mucopolysaccharides (Behnke 1968 Shea 1971
-on 1977)

-ould be noted that a neutralized lanthanum solution contains both ionic
anum and lanthanum in colloidal form (Schatzki & Newsome 1975) Lanthanum
irs mainly as a tracer or mainly as a stain dependent partly on pH of the
on partly on the concentration of lanthanum
e present paper describes some results of the application of lanthanum used as a
dal tracer and as an ionic stain on PE material on the anterior lens surface

Material and Methods

a erial from the peripheral band and the central d sc on the anterior lens capsule has
stud ed The lenses were cataractous and they were obta ned by cataract cryo-extraction
is found by sl t lamp exam nation prior to the operation
e lenses were suspended directly n a solut on of collid ne buffered osm um tetrox de
ared as described by Bennet & Luft 1959) contain ng 2 to 5% lanthanum n trate The
s were f xed n this solution for 2 to 2? h Five other lenses were f rst suspended in a 2 to
solution of lan hanum nitrate to which 0 01 N NaOH had been slowly added until pH
about 7 8 and a fa nt opacity could be observed After ½ to 1 h the lenses were suspended
coll d ne buffered solut on of osm um tetrox de as described abo e n these cases 1%
anum n trate was added
ter f xation the lenses were dehydrated in graded ethanol solutions Specimens were
ared from the anterior lens capsule at the site of the peripheral band and the central
The s e of the cryo extractor was avo ded The specimens were embedded in Epon 812
sectioned with a Reichert Ultracut m crotome Ultrath n sections were contrasted with
l ne lead or an aqueous solut on of uranyl acetate or both Electron m croscopy was
ormed w th a Jeol 100 B electron microscope



F g 1

Pseudo-exfol ation excrescences on the anterior lens surface Lan hanum trac pa adhere to the surface of the excrescences The area n m cr graph B s a o micrograph A (as ind cated by angles) U ncontrasted section LC Lens capsule
A x 6 00 B x 14 00

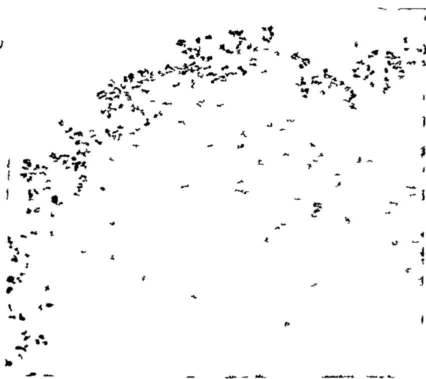


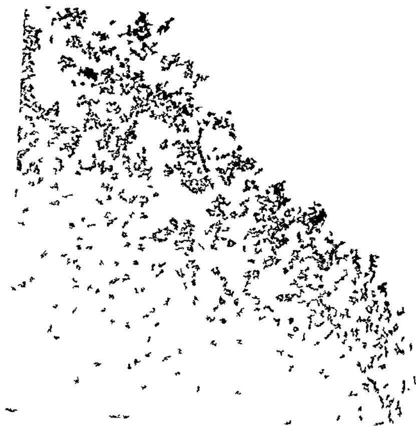
Fig 2

lo-exfoliation material Lanthanum tracer particles The larger particles adhere to the ce of the excrescence the smallest particles have penetrated sparsely into the superficial layer of the material Uncontrasted section x 43 800

Results

he specimens which had been treated with lanthanum at high concentration or at a pH near 7 8 the effects of lanthanum were revealed mainly by the ence of distinct lanthanum tracer particles while ionic staining was less obvious particles were also electron-dense in uncontrasted sections and micrographs n uncontrasted sections were particularly suited for the demonstration of the er Particles of different sizes were present, with diameter from about 50 nm to than 5 nm (Figs 1 and 2)

n obvious pattern was found in the distribution of the tracer particles relative to PE excrescences The main part of the particles and all those which were larger n 5 nm were located within a narrow zone along the surface of the PE material gs 1 and 2) Evidently colloidal particles of lanthanum hydroxide had adhered



F g 3
Pseudo-exfoliation material The superf cial layer (1 ° µm) of the excrescences is ionic lanthanum wh ch has not penetrated nto the deeper parts Uncontrasted x °9 000

to this surface during the preparation and none of the larger partic penetrated into the PE material

By using higher magnification it could be seen that a few small tracer part 5 nm) were localized in the superficial parts of the PE material (F g °) These particles had a tendency to be located along the PE fibrils and to a interfibrillar spaces Except for this tendency their d stribution seemed random

The specimens which had been treated with lanthanum at a lower concen and or at a lower pH demonstrated a somewhat different p cture La tracer particles were present only to a minor degree and the few particles had distinct appearence and form However in these specimens the trea lanthanum was revealed by lanthanum staining of parts of the PE ma erial w

cases the presence of lanthanum is best demonstrated in uncontrasted is (Fig 3)

i lanthanum staining was clearly limited to superficial parts of the PE cences Beyond a depth of 1 2 µm no effects of lanthanum could be found egree of staining decreased gradually from the surface inwards however the r between stained and unstained PE material was usually quite marked

PE fibrils were denser and thicker in the stained parts of the material and iad a more ragged outline as compared with the fibrils of the unstained areas instained electron lucent areas between the fibrils were reduced in size Near irface of the excrescences most of the material was stained and the fibrils be distinguished only with difficulty The lanthanum staining was not genous and by higher magnification it could be seen that the staining ined or consisted of numerous small dense more or less confluenting spots of ular form

some of the specimens the staining with lanthanum did not reveal further rmation about the ultrastructure of the PE material However in other mens details concerning subfilaments and crossbands of the fibrils appeared in of the PE excrescences This will be dealt with in a subsequent paper

Discussion

ectron micrographs of PE material which has been prepared by conventional iods the interfibrillar spaces do not appear to contain any material However listribution of the lanthanum tracer particles as found in this work and shown ie Figs 1 and 2 demonstrates beyond doubt that the interfibrillar spaces are d with a substance which prevents most of the tracer particles from entering the PE material The concept of an interfibrillar matrix as part of the PE erial (Davanger & Pedersen 1975 Davanger 1977 1978) is thereby confirmed s matrix is usually electron lucent and invisible by electron microscopy

While the main part of the lanthanum tracer particles are excluded from the erial particles with a diameter less than about 5 nm are sparsely admitted into uperficial parts (Fig 2) Accordingly this size seems to represent the limit of lusion of lanthanum tracer particles from the PE material In this connection it uld be noted that the molecular tracer horse radish peroxidase with a molecular meter of about 4 5 nm (Vegge et al 1971) was excluded from the material vanger & Pedersen 1975) while the smaller tracer microperoxidase (diameter out 2 nm (Feder 1971)) was admitted only into its superficial parts (Davanger 78) It may be presumed that tracers are totally or partially excluded partly for

sterical reasons but that also other factors such as electrostatical forces involved

According to several authors (Behnke 1968 Shea 1971 Johnson 1977) lanthanum has affinity to proteoglycans acid mucopolysaccharides. The staining with lanthanum of the superficial parts of the PE material demonstrated supports the concept that the material consists of or contains such substances

It has been reported that lanthanum staining is found at or near the tissue fragments while the deeper layers remain unstained (Lesseps 1967) abscence of lanthanum staining beyond the surface layers has been considered caused by poor penetration of lanthanum ions in most tissues In the present lanthanum staining was confined to the superficial 1 2 µm of the PE material Obviously the penetration of lanthanum ions is very restricted in the PE material and more restricted than in most tissues This is another demonstration of penetrability as one of the characteristics of the PE material

Poor penetrability of lanthanum has also been noted for amyloid (Sørensen & Bari 1968) Accordingly the partial exclusion of lanthanum is one of the properties which the PE material has in common with amyloid

References

Behnke O (1968) Electron microscopic observations on the surface coating of human platelets *J Ultrastruct Res 24* 51

Bennet H S & Luft J H (1959) s-collidine as a basis for buffering fixatives *J biophys biochem Cytol 6* 113–114

Davanger M & Pedersen O Ø (1975) Pseudo-exfoliation material on the anterior lens surface Demonstration and examination of an interfibrillar ground substance *Acta ophthal (Kbh) 53* 3–18

Davanger M (1977) On the molecular composition and physico-chemical properties of the pseudo exfoliation material *Acta ophthal (Kbh) 55* 621–633

Davanger M (1978) On the interfibrillar matrix of the pseudo-exfoliation material *Acta ophthal (Kbh) 56* 233–240

Feder N (1971) Microperoxidase An ultrastructural tracer of low molecular weight *J cell Biol 51* 339–343

Johnson K E (1977) Extracellular matrix synthesis in blastula and gastrula stages of normal and hybrid frog embryos I Thluidine blue and lanthanum staining *J cell Sci* 313–322

Lesseps R J (1967) The removal by phospholipase C of a layer of lanthanum staining material external to the cell membrane in embryonic chick cells *J cell Biol 34* 1 5

Revel J P & Karnovsky M J (1967) Hexagonal array of subunits in intercellular junctions of the mouse heart and liver *J cell Biol 33* C7–C12

Schatzki P F & Newsome A (1975) Neutralize 1 lanthanum solution a largely non ultrastructural tracer *Stain Technology 50* 171–178

Shea S M (1971) Lanthanum staining of the surface coat of cells *J cell Biol 51* 611

ı n G D & Barı W A (1968) Murıne amyloid deposıts and cellular relatıon hıps In lema E Ruınen L scholten J H & Cohen A S eds Amyloıdosıs p 59 Excerpta ca, Amsterdam
T Wınther F Ø & Olsen B R (1971) Horseradısh peroxıdase ın plasma studıed by ltratıon *Hıstochemıe* 28 16–22

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ON THE ULTRASTRUCTURE AND THE FORMATION OF PSEUDO EXFOLIATION MATERIAL

BY

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Pseudo-exfoliation (PE) excrescences on the anterior lens surface were studied by electron microscopy In some cases the superficial layer of the excrescences consisted of a meshwork of fibrils and filamentous subfibrillar units. It could be clearly seen that the fibrils were formed by lateral aggregation of filamentous units Both the filaments and the fibrils had crossbands regularly spaced at 17 nm In some fibrils every third crossband was fainter than the neighbouring crossbands Thereby a secondary periodicity appeared, the new period consisting of three crossbands in the order dense faint-dense. The length of this period was 17×3=51 nm i.e. the same as the distance between the crossbands of conventional PE fibrils All transitional forms between the fibrils with 17 nm periodicity and the conventional PE fibrils were found, and there was a gradual transition between the material described and the conventional PE material It is suggested that the material on the surface of the PE excrescences represent newly formed PE material This may be formed by condensation and linear polymerization of two kinds of units corresponding to the dense and the faint crossbands

Key words pseudo-exfoliation – fibrils – filaments – crossbands.

When examined by electron microscopy the pseudo-exfoliation (PE) fibrils constitute the characteristic element of the PE material Several authors have assumed these fibrils are composed of filamentous subunits (Ringvold & Husby Davanger 1977 Davanger & Hovig 1978 Dark et al. 1977) but a more demonstration and description of these subunits has not been given. Evidence has been presented indicating that linear filamentous units are also present in the interfibrillar spaces and it has been suggested that these filaments are of the same kind as those constituting the PE fibrils (Davanger 1977 1978)

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Fig 1

hwork of filaments and fibrils at the superficial layer of pseudo-exfoliation excrescences ,z fibrils are obviously formed by lateral aggregation of the filaments Both the filaments id the fibrils have a 17 nm periodicity Section contrasted with lead and uranyl X 36 600

everal authors have described crossbands as a feature of the PE fibrils Usually e crossbands are faint and often difficult to discern They present themselves inly as faint periodic variations of the thickness in the fibrils However as the line of the fibrils usually appears rather blurred and woollen the crossbanding is t clearly seen in most fibrils The distance between the crossbands has been easured to 51 56 nm (Bertelsen et al 1964) 40-56 nm (Ringvold 1969) 50-55 nm 25 30 nm (Davanger 1977 Davanger & Hovig 1978) or 20 nm (Dark et al 1977) During electron microscopy of PE material which had been stained en bloc with


A
B
C
D
E
F
G

lanthanum it was observed that in parts of the PE excrescences filamentous ...nillar units were clearly visible The filaments were found also in the ...brillar spaces and it could be clearly seen that the fibrils were composed of ...ntous units Further the study of these specimens revealed new details of the ...riodicity and the crossbanding of the PE fibrils

...the present paper these findings will be demonstrated described and ...sed

Material and Methods

...naterial consists of five lenses with PE The lenses were cataractous and they ...obtained by cataract cryo-extraction The lenses were suspended in a solution ...llidine buffered *osmium tetroxide containing 2 to 5% lanthanum nitrate* ...ts of the electron microscopical examination of these lenses have been ...ibed from another point of view in a recent publication (Davanger 1980) ...ls of the preparation and methods of examination are described in that paper

Results

PE excrescences consisted mainly of PE material with the conventional ...arance Most of the surface layer of the excrescences was stained by ionic ...anum as it has been described in a recent paper (Davanger 1980) However in ...of the five lenses the material had a different and typical appearance in parts ...e PE excrescences mainly at their surface and especially near their apices In ...ollowing the morphology of these parts of the excrescences will be described

...he electron microscopical picture (Fig 1) was dominated by two distinct and ...acteristic morphological elements One of these was a filament with a uniform ...kness of 10 nm and a lenght in the sections up to 1 µm These filaments were ...ively straight or slightly bent The filaments had an obvious periodic construc ...with alternating dark and light zones of about equal length The repeat period ...isted accordingly of one dark and one light zone This period was 17 nm long

...he other *morphological element was a fibril with marked and characteristic* ...sbands Although these fibrils had no longitudinal striation they were obviously ...ned by lateral aggregation of the filaments recently described Several features ...port this concept Some filaments were part of a fibril for only a portion of their

Fig 2

...ils in the superficial layer of pseudo-exfoliation excrescences Crossbands 17 nm apart ...anged in the order dense faint-dense-dense faint-dense etc Secondary periodicity of 17 ...× 3 = 51 nm Sections contrasted with lead and uranyl A × 45 100 B × 55 500 C × ...54 500 D × 52 000 E × 79 500 F × 84 000 G × 118 000

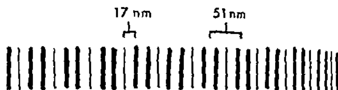


Fig 3

Schematic drawing of a pseudo-exfoliation fibril Crossbands 1ι nm ap... periodicity The crossbands are arranged in the order dense faint-dense-dense f... etc A secondary period of 17 nm × 3= 51 nm contains one dense one faint ... crossband

length One filament might be entangled with more than one fibril, whe... irregular meshwork was formed in which the fibrils formed the crossl... site of junction between a fibril and a filament, it could be seen that the ... added to the thickness of the fibril As will be described in the follo... filaments and the fibrils had the same periodicity

These fibrils were randomly distributed in relation to each other exc... tendency to form irregular groups in which the individual fibrils ... incompletely separated The length of the fibrils as seen in the sections ... to 2 µm Also the thickness varied a typical diameter being 50 nm

The fibrils concerned were conspicuously crossbanded with alternating d... light lines crossing the fibrils at a right angle The basic repeat period was ... the same as the period of the filaments in the spaces between the fibrils ... of junction between a fibril and a filament the dark and light zones of the ... were aligned in phase with the alternating dark and light crossbands of th... Obviously these crossbands were the result of the alignment of the alterna... and light zones of the filaments of which the fibrils were composed.

A closer examination revealed that in many fibrils the density of the cro... varied in a systematic manner Every third crossband was slightly or ... fainter than the adjoining crossbands (Fig 2) Accordingly the crossba... arranged in the order dense faint-dense-dense faint-dense etc. A secondar... dicity appeared consisting of three of the original periods that is, the le... new period was 17×3=51 nm (Fig 3) This is the same as the period leng... conventional PE fibrils

In those fibrils where the 51 nm periodicity was dominant the ... crossbands in each period tended to be longer than the faint crossb... accordingly the dense crossbands protruded slightly beyond the general ... of the fibril In some of those fibrils the white lines separating two neig... dark crossbands were thin irregular and not easily seen The appearance ... fibrils was not much different from the appearance of the conventional P...

eighbouring dense crossbands tended to fuse to form one crossband which en mainly as a thickening of the fibril Such thickenings were regularly spaced ım

ording to the above all transitional forms could be found between the fibrils ure 17 nm periodicity and the conventional PE fibrils with 51 nm periodicity ping with this there was usually no sharp boundary between the conventional terial and the material consisting of a meshwork of filaments and fibrils with ı periodicity as described above

Discussion

reatment with lanthanum may have enhanced the features described in this and made them more conspicous but lanthanum is probably not a condition ieir demonstration The presence of filaments as well as fibrils in the PE ıal has been described before Likewise the coalescence of filaments into PE has been presumed or demonstrated by several authors (Ringvold & Husby Davanger 1977 1978ab Dark et al 1978) However a detailed demonstration ; process has not been presented before

ne of the fibrils shown in the present paper have many characteristics in ıon with the fibrils found by Ringvold (1970a) by negative staining of PE ıal This concerns also the crossbands and the periodicity It should be noted ibrils remarkably like those described above have been found by Ringvold b) in sections of iris tissue from old patients operated for senile cataract al signs of the PE syndrome had not been found in these patients

e meshwork of filaments and fibrils on which the present work has concen l is clearly a part of the PE excrescences and the PE material although its ırance differs in details from that conventionally described for PE material relationship between the conventional PE fibrils (period length 51 nm) and with a 17 nm periodicity is underlined by the presence of transitional forms een the two types

s reasonable to look at this transition from a dynamical point of view that is to der the different morphology at different locations of the PE excrescences as senting different stages in the formation of the PE fibrils and the PE material 4) The PE material may be thought to be formed by a gradual condensation ıe anterior lens surface and other surfaces of substances which have been ved in the aqueous The excrescences must be presumed to increase in size by ıccumulation of new material on their surface The material which has been onstrated is thought to represent PE material in an early stage of formation

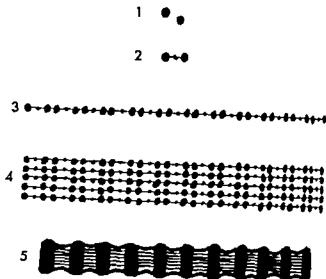


Fig 4

Formation of a pseudo exfoliation fibril (hypothetical) 1 A solution of two molecular units dense and faint 2 Two dense and one faint unit combine to monomer of the fibril 3 Monomers combine end to end to form a filament are seen regularly spaced at 17 nm 4 Immature PE fibrils are formed by lateral a of filaments Crossbands (dense and faint) are formed 17 nm apart, by the alignm basic units 5 Mature PE fibril The fusion of two adjacent dense crossbands disappearance of the faint crossbands produce a periodicity of 17 nm × 3 51

Although the real process may be different it is tempting to demonst simple and schematic form a possible mechanism for the formation of th (Fig 4) The basic units may be of two kinds of which one will develop dense crossbands and the other into the faint crossbands The two differ of units may be thought to combine to form a linear symmetrical block cons one dense one faint and one dense unit This block is the monomer from the fibrils are formed by polymerization The monomers attach to each other end thereby forming a filament Several filaments combine by lateral agg to form bundles During this process the basic units align to form the cross the primary fibrils 17 nm apart This primary periodicity changes gradually 51 nm periodicity as described earlier At the same time the original thad condenses into the conventional PE fibril and the electron lucent zones be the original crossbands disappear

The immature PE material characterized by the presence of filaments and periodicity is formed at the surface of the PE excrescences The transition fro material into conventional PE material may be thought of as a maturation p

may be analogous with the aging process which takes place during the first after the formation by polymerization of collagen fibrils (Gross 1961) The ration of collagen has been explained by increasing perfection of fit between ubunits as they gradually pack together As in the case of collagen the osed maturation process of PE material seems to lead to the formation of a and insoluble material

References

lsen T I Drabløs P A & Flood P R (1964) The so-called senile exfoliation udoexfoliation) of the anterior lens capsule a product of the lens epithelium nllopathia epitheliocapsularis *Acta ophthal (Kbh) 42* 1096 1113

A J Streeten B W & Cornwall C C (1977) Pseudoexfoliative disease of the lens A y in electron microscopy and histochemistry *Brit J Ophthal 61* 462–472

nger M (1977) On the molecular composition and physico-chemical properties of the udo-exfoliation material *Acta phthal (Kbh) 55* 6?1–633

nger M (19 8) On the interfibrillar matrix of the pseudo-exfoliation material *Acta thal. (Kbh) 56* 233–240

nger M (1980) Pseudo-exfoliation material Electron microscopy after the application of ithanum as tracer particles and ionic stain *Acta ophthal (Kbh) 58* 513 520

nger M & Hovig T (1978) Pseudo-exfoliation fibrils examined by negative staining *ta ophthal (Kbh) 56* 226–232

ss J (1961) Collagen *Scientific American* May 1961 1?0–130

nold A (1969) Electron microscopy of the wall of iris vessels in eyes with and without foliation syndrome (Pseudoexfoliation of the lens capsule) *Virchows Arch. Abt A Path nat. 348* 328–341

gold A (1970a) Ultrastructure of exfoliation material (busacca deposits) *Virchows Arch. bt A Path. Anat 350* 95–104

gold A (1970b) Ultrastructure of the extracellular components in human iris *Z ellforsch. 109* 306–315

gold A & Husby G (1973) Pseudo-exfoliation material – an amyloid like substance *Exp ye Res 17* 289–299

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INDOCYANINE GREEN FLUORESCENCE ANGIOGRAPHY

BY

LEA HYVARINEN[1] and ROBERT W FLOWER

Indocyan ne green (ICG) fluorescence ang ography has been further refined for use n both laboratory and cl n cal n estigations In the p esent modification of the Ze ss fundus camera all lenses except the aspherical objective lens have been specially ant reflect on coated to ncrease l ght ran mis ion in the spectral region around 800 nm A 300 watt nd um od de lamp continuous light source has replaced the con entional xenon flash lamp This light source produces a ret nal irrad ance of 265 mw and therefo e restricts retinal exposure time to 11 9 seconds but that t me s more han adequate to record passage of dye through the choro d Spatial resolution of the fundus on the film has been ncreased from 11 7 m crons to 7 4 m crons
W th these techn cal ref nements the choro dal circula ion can be studied at frames per second wh ch is adequa e to document the ery rapid movement of blood through the asculature ICG angiography may change our in terpretat ons of choro dal circulatory phenomena wh ch are now based on fluorescein angiography and t clearly s an effecti e tool n labora ory (experimental) n est gat ons

Key words ndocyan ne green fluorescence – angiograph c studies of the eye choro dal circulat on

Sodium fluorescein angiography has been an important part of ophthalmic armamentarium for well over a decade now and its cl n cal diagnostic ... retinal vascular diseases cannot be impugned Howe er its usefulness in s... bloodflow dynamics is l m ted especially n the choroid where transmission of vis ble light wavelengths is poor and extravasat on of fluorescein d e readily ...

Rece ved December 7 19 9

are even instances in which misinterpretation of fluorescein angiograms may .d to erroneous conclusions about choroidal bloodflow (Flower 1972 1980)

elopment of indocyanine green (ICG) fluorescence angiography was initially d solely as a way to obviate the limitations imposed by fluorescein dye during mental studies of choroidal bloodflow dynamics It was serendipitous that on in development of the technique it became evident that ICC angiography be used safely and routinely on human subjects as well Clinical ICG graphy has been performed since about late 1973 and the data obtained have invaluable to refinement of the technique The accumulated angiographic ial is still insufficient to warrant interpretation of choroidal circulatory omena in pathological conditions However some observations can be repor

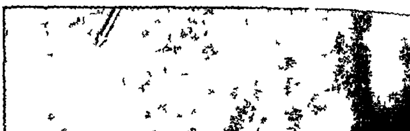
th ICG absorption angiography and the early method of fluorescence choroi ngiography have been described in detail before (Flower 1972a,b Flower & heimer 1973 1976 Flower 1976) therefore it is the refinements and resulting ovements in spatial and temporal resolution achieved since these which are ibed below

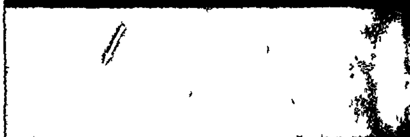
Technique

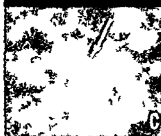
ng the development of the new camera for ICG angiography approximately ICG human angiograms were made at the University of Oulu Department of thalmology and 480 in the Wilmer Ophthalmological Institute ICG and escein angiograms were done a few minutes apart Injection of ICG dye was e via a 3-way cannula followed immediately by a saline flush (Flower 1973) No gic or vasovagal reactions occured and none of the patients were discomforted ie illumination used for ICG near infrared photography

'0 ICG angiograms of rhesus monkeys were made at the Wilmer Ophthal ogical Institute The injection technique was identical with that in human es except that smaller volumes were injected and all animals were anesthetized i halothane

uorescence ICG angiography is performed in much the same way as fluorescein ography the major difference being that ICG angiography utilizes near ired light wavelengths while fluorescein utilizes light wavelengths in the visible on of the spectrum Descriptions of the absorption and emission ICG dye tra as well as characteristics of the photographic film and excitation and barrier rs used in choroidal angiography have been previously published (Flower & hheimer 1973 1976) Briefly the advantages of ICG dye in choroidal angio- phy are that there is no extravasation from the choriocapillaris, that it absorbs






C


D


F


G



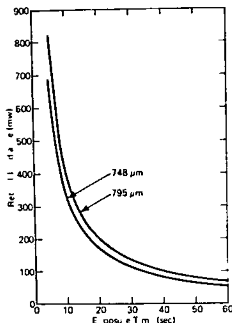


Fig 1

ph indicating maximum level of safe retinal irradiance as a function of exposure time

and fluoresces in a spectral region where retinal and choroidal pigments are transparent and that its long wavelengths of emitted light are more than six less scattered by the ocular media than the shorter visible light wavelengths ed by fluorescein Its principal disadvantage is that it does not fluoresce ently Whereas the quantam efficiency of fluorescein dye in blood is nearly 1 of ICG dye is only 0 13 and if the relative fluorescence intensity of fluorescein arbitrarily set at 1 that of ICG is 25 times less Therefore developing the umentation for choroidal angiography essentially has been an exercise in izing ability to record the fluorescent light energy emitted by ICG dye in the r blood vessels

Fig 2

consecutive frames of a 20 frame per second ICG fluorescence angiogram made of an rhesus monkey Arrows indicate the location of the same individual choroicapillaris e throughout the sequence In frames A D the arterial feeder of the lobule can be ified In frames D-F to the left of the arrow the drainage enules into which the lobule es can be seen Note that in frame A F the lobule appears white as it fills with dye and appears black in frames G-J where it has essentially emptied Maximum filling of the lobule occurred by frame D indicating a filling time of only 0 2 seconds

The lenses of the fundus camera are normally antireflection coa transmit light throughout the visible spectrum with maximum curring at about 530 nm wavelength However near 800 nm was ICG fluorescence occurs the measured loss of light energy at e about 4% (the loss nominally occuring at most wavelengths when elements are used) By antireflection coating lens elements specificall wavelength this loss can be reduced to as little as 0 3% per lens surface done to all lenses in the Zeiss fundus camera imaging optics except objective lens which is normally uncoated Providing one of the aux tion lenses is not used there are 14 lens surfaces in the fundus camer optics At 800 nm wavelength with the original lens coatings total light was 0 960^{14}=0 560 or 56% with proper antireflection coatings total became 0 997^{14}=0 959 or 96% which amounts to 40% more light film exposures

The effective aperture stop in the Zeiss camera is the hole drilled diagonal mirror located between the aspherical objective lens and the wheel Normally this hole is 5 mm in diameter but by enlarging it to 1 cm much light can pass through the imaging optics to the pho Reduction of this diagonal mirror surface which reflects light into the results in an 11% decrease of 800 nm wavelength excitation light energy regained by replacing the aluminum coatings on both diagonal mi illumination optics with quartz-clad silver Added to the gain in t achived by using better lens coatings a total gain of 5 7 times in light transmission at 800 nm wavelength makes it possible to photograph the the 2 5 times magnification of the standard Zeiss fundus camera

Of equal importance is improving temporal resolution of the rapid dye filling sequence of events Since no flash lamp light source is a be re cycled at a sufficiently high rate and yet deliver enough light energ flash to perform ICG angiography a continuous light source was installed I a 150 watt quartz halogen lamp was used and in order to increase the a intensity an adjustable mirror was also installed behind the lamp More re used a 300 watt indium iodide lamp which has a much larger in light component at 800 nm wavelength Caution must be exercised in using continuous light source to insure that retinal irradiance does not For the approximate 35 degree fundus area illuminated by the Zeiss fundus and for the light wavelengths required to excite ICG dye to flu maximum permissible exposure of the retina is 3160 mw seconds (A National Standard for the safe use of lasers 1973) Retinal irradiance as function of continuous exposure time in Fig 1 The indium iodide light produces a retinal irradiance of 265 mw consequently an exposure tim

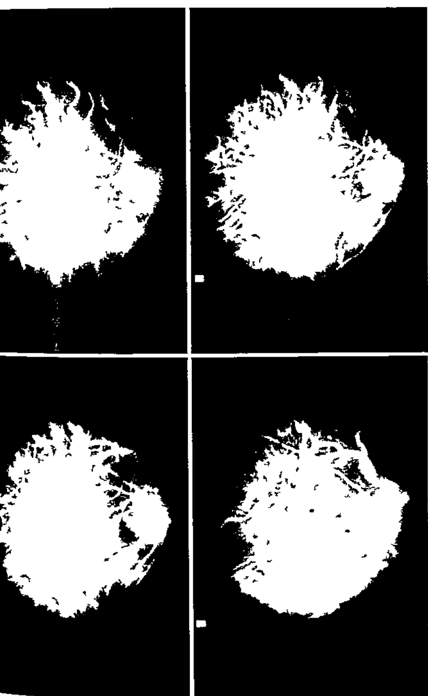


Fig 3
angiograms with unusually good vis bility of both arteries (A B) and eins of choro d (C D)

more than 11 9 seconds is permitted but this is more than adequate to passage of dye through the choroidal circulation

The brighter light source coupled with improved light transmission the camera optics makes it easy to now record angiograms at rates up second this compares favorably with the 4 or 5 frames per second achieved At the same time spatial resolution of the fundus on film was from 11 7 microns to 7 4 microns which is nearly equal to that achieved in fluorescein angiography

During the development of the new camera several hundred angiog made to test the different improvements and the clinical application of the In these angiograms a number of interesting phenomena were recorded which are reported in this paper

Results

Animal experiments

We have recently succeeded in photographing the passage of ICC dye thr choroid at 20 frames per second The ten consecutive frames in Fig visualization of a sharp dye wavefront moving through the entire c vasculature of an adult rhesus monkey eye following retrograde injection than 0 05 ml of dye into the contralateral common carotid artery The that the average time required for dye transit across individual cho lobules is on the average 1/5 second The dye wavefront may be easily fo the particular lobule indicated by the arrow throughout the sequence The angiograms and others made the same way confirm and even refine chorm bloodflow measurements made earlier But more significantly in the cont present paper they demonstrate the necessity for using high speed angiog study the choroidal circulation Obviously subtle changes in choroidal bl could be completely missed in angiograms of less temporal or spatial resol

Human Studies

Although the choroid is nearly transparent to both those wavelengths of to excite ICG dye to fluorescence and those emitted by the dye there wa variation in visibility of choroidal vessels among different individuals The for this variation are not apparent choroidal vessels were quite often ve visualized in young healthy persons with no known choroidal patholgy visibility was not due simply to poor photographic technique resolution details was good In less than one third of the angiograms were choroid seen as clearly as those in Fig 3 where both the short ciliary arteries

Fg 4
) is more reliable than fluorescein for measurement of dye appearance time in choroid
ICG fluorescence is also attenuated by the pigment. Note that the fluorescence intensity
ve in the cilioretinal artery (cra) is higher than in nearby choroidal vessels although dye
concentrations in these vessels most probably are identical

nches and later the choroidal veins are well defined smaller wein branches and nocapillaris are not visualized

or measurement of dye appearance time in the choroidal vasculature ICG is re reliable than fluorescein because it is more easily seen through the retinal and oroidal pigment and it does not become extravasated ICG fluorescence wever can be attenuated by pigment as demonstrated in Fig 4 First appearance dye traces in the cilioretinal artery is seen in the frame preceeding Fig 4 whereas e retinal vessels are barely visible Note that the fluorescence itensity of dye in the ioretinal artery is higher than that in the nearby choroidal vessels although dye ncentration in both these vessels would be expected to be nearly identical

Blockage of ICG fluorescence is similar to that observed with fluorescein blood pigment clumps in retina can produce distinct areas of reduced or non iorescence in angiograms similarly the egg yolk substance in Best s disease ocks choroidal ICG fluorescence But on the other hand ICG angiography does

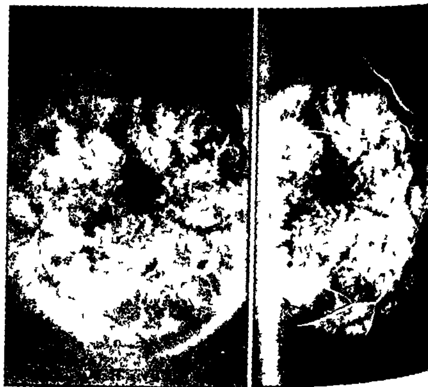


Fig 5

In ICG-angiograms (A B) there is an area of decreased dye fluorescence (arrow) [illegible] detectable in corresponding fluorescein angiograms (C, D) Times measured from [illegible] appearance of the dye 1 6 seconds (A C) 3 [illegible] seconds (B D)



Fig 6

...luorescein angiogram of a large submacular neovascularization with a large feeding ... (arrow) The draining vein wraps around the artery and its proximal part cannot be seen because of diffuse fluorescence near the disc

...n the ICG-angiogram the vein is seen not to follow the artery to the disc margin and thus photocoagulation was placed close to the edge of the disc

...etimes reveal circulatory changes in choroid which are not detectable in ...esponding fluorescein angiograms because of the masking effect of fluorescein ...h diffuses from the choriocapillaris into the intervascular space (Flower et al ...7 Hyvarinen & Maumenee 1971) Figs 5A and 5B show an area of delayed ...ng in the choroid but in corresponding fluorescein angiograms (Figs 5C and ...) no such area of delayed filling is detectable

...o far ICG angiography has not been used for clinical diagnosis but the findings ... occasionally affected clinical decisions In Fig 6A a large submacular neovas...arization with a large feeding artery is shown The draining vein could not be ...n in the fluorescein angiograms clearly enough to warrant photocoagulation of ... feeder at the disc margin In the ICG angiogram (Fig 6B) the vein can be seen ... follow the artery only half way to the disc Based upon this observation ...otocoagulation was made at the disc margin and the neovascularization collapsed ...hout danger of venous bleeding

Discussion

Development of ICG angiography has been ongoing for several years. The method which used adaptors and an otherwise unmodified Zeiss fundus camera given some insight into the choroidal circulation (Craandijk & Van Beek; Forsius et al 1977). The technical refinements now make possible ... choroidal angiography in clinical investigations. Before it can be used as a diagnostic tool, however, a fairly large number of studies are needed to determine basic interpretations of different circulatory patterns. At the present time ... angiography has already demonstrated that fluorescein angiography can give a false impression of circulatory status in some clinical conditions.

References

American National Standard for the Safe Use of Lasers publication ANSI Z1... (1973) by the American National Standards Institutes Inc New York.

Craandijk A & Van Beek C A (1976) Indocyanine green fluorescence angiography of the choroid. *Brit J Ophthal 60* 377–385

Flower R W (1972a) Infrared absorption angiography of the choroid and some observations on the effects of high intraocular pressures. *Amer J Ophthal 74* 600–614

Flower R W (1972b) Simple adaptors for fast conversion of a fundus camera for rapidsequence ICG fluorescence choroidal angiography. *J Biol Photogr Ass ...*

Flower R W & Hochheimer B F (1973) A clinical technique and apparatus for simultaneous angiography of the separate retinal and choroidal circulations. *Invest Ophthal 12* ...

Flower R W (1973) Injection technique for indocyanine green and sodium fluorescein angiography of the eye. *Invest Ophthal 12* 881–895

Flower R W & Hochheimer B F (1976) Indocyanine green dye fluorescence and infrared absorption choroidal angiography performed simultaneously with fluorescein ... *Johns Hopkins Med J 138* 33–42

Flower R W (1976) High Speed human choroidal angiography using indocyanine green and a continuous light source. In DeLaey J J (Ed) International Symposium on Fluorescein Angiography. Documenta Ophthalmologica Proceedings Series ... 59–64 Dr W Junk bv the Hague

Flower R W Speros P & Kenyon K R (1977) Electroretinographic changes and ... defects in a case of central retinal artery occlusion. *Amer J Ophthal 83* 451–4..

Flower R W (1980) Choroidal fluorescent dye filling patterns: a comparison of ICG and fluorescein angiograms (To be published)

Forsius H Hyvarinen L Nieminen H & Flower R W (1977) Fluorescein and indocyanine green fluorescence angiography in study of affected males and in female carriers of choroideremia. *Acta ophthal (Kbh) 55* 459–470

Hyvarinen L & Maumenee A E (1971) Interpretation of choroidal fluorescence ... P (Ed) Proc int Symp Fluorescein Angiography Albi (1969) pp ... Basel New York

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ELECTRORETINOGRAM (ERG) AND VISUAL EVOKED RESPONSE (VER) STUDIES IN PATIENTS WITH OPTIC DISC DRUSEN

BY

EILA MUSTONEN ILMAR SULG and TAPANI KALLANRANTA

Non-corneal ERGs recorded from infraorbital skin electrodes to flash stimulation and mid-occipital and parasagittal VERs to both flash stimulation and pattern reversal were performed in 26 patients with optic disc drusen. ERGs were normal in all patients The mean VER amplitude was lower in the eyes with optic disc drusen than the mean amplitude of VERs in the normals but the interindividual variation was also so great in normals that the difference was not significant. The waveform of the major positive peak was quite often broad or split. VER latencies were usually in normal range although the visual field defects could be rather severe Some other cause was present when the major positive peak was delayed

Key words drusen ERG – half field stimulation – hyaline bodies optic disc – perimetry – skin electrodes VER.

ic disc drusen are anomalous homogeneous often calcified hyaline bodies of optic nerve heads situated in front of the lamina cribrosa They can bring about al field defects presumably by compression causing atrophy of the adjacent ve fibres or on a vascular ischaemic basis Visual fields may reveal enlargement he blind spot nerve fibre bundle arcuate scotomas nasal sector or quadrant cts or peculiar irregular concentric contractions (Lorentzen 1966 Savino et al 9) Central visual acuity usually remains normal (Lansche & Rucker 1957 ker & Kearns 1961 Pietruschka & Priess 1973 Erkkila 1977 Fotzsch et al 8 Rosenberg et al 1979)

eived December 31 1979

VER has been found to be very sensitive for detecting demyelinated [illegible] optic nerves in multiple sclerosis (Halliday et al 1972 19[illegible] [illegible] Asselman et al 1975 Regan et al 1975 Wildberger 19[illegible] Lowitzsch et al Bynke et al 1977 Chain et al 1977 Celesia & Daly 1977 [illegible] Zeese 1977 Hennerici et al 1977 Hoeppner 1978 Shahrokhi et al [illegible] when visual acuity visual fields and optic discs are normal and there is [illegible] retrobulbar neuritis or papillitis Increase in the latency of the potentials [illegible] the occipital cortex by pattern stimulation of the retina is the typical [illegible] have also been demonstrated by flash stimulation (Richey et al 19[illegible] [illegible] Enns 1972 Feinsod & Hoyt 1975 Paty et al 1976 Ellenberger & Ziegler [illegible] multiple sclerosis

VER delays have been found also in spinocerebellar degeneration [illegible] atrophy in dominantly inherited isolated optic atrophy and in compress[illegible] of the optic nerve (Halliday et al 1973 Asselman et al 19[illegible]) as well as [illegible] optic neuropathy (Hennerici et al 1977) and in Leber hereditary optic [illegible] (Nikoskelainen et al 1977) Bornstein (197[illegible]) observed delayed responses [illegible] atrophy trauma compression and vascular disease Delayed pattern respon[illegible] also been reported in glaucoma (Cappin & Nissim 1975 Bartl 19[illegible])

Compressive lesions of the anterior visual pathways have been found to [illegible] abnormal pattern responses (Halliday et al 1976) even when other clinical [illegible] visual impairment were absent and visual acuity visual fields and [illegible] unaffected but the character of the changes was different from that seen [illegible] on primary demyelinating disease The incidence of delayed responses was [illegible] much lower and the magnitude of the delays smaller than with multiple [illegible] Absent responses and abnormalities of the waveform of the responses were [illegible]

We have not found in the literature reports of simultaneous ERG and [illegible] studies in patients with optic disc drusen except one patient mentioned by [illegible] al (1977) and a short comment by Neetens & Burvenich (1977) upon VER [illegible] diagnosis of optic disc drusen As a part of more comprehensive examina[illegible] patients with optic disc drusen non-corneal ERGs to flash stimula[illegible] mid occipital and parasagittal VERs both to flash stimulation and pattern [illegible] were performed in 26 patients and the results are presented in this report

Material and Methods

In 26 patients (4 with unilateral and 22 with bilateral optic disc drusen) [illegible] infraorbital ERGs to flash stimulation and mid occipital and parasagittal VERs to [illegible] stimulation and pattern reversal were performed Seventeen patients with [illegible] were also examined by half field stimulation method (Barrett et al 1[illegible]) [illegible] occipital electrodes

od was the same as n our report of skin electrodes n ERG (Mustonen & Sulg 1980) *re adaptation in weak room llum nation (2 5-3 lux) for 25 m n followed by 5 m n in* ss the patient was st mulated with 10 flashes (1500 lux) of 10 mseconds durat on and y of 0 2 joule from an Elema S emens photostimulator (EMT 92) with a lighted area x 325 mm giving wh te l ght flashes with 15 second intervals 20 cm in front of the s eyes Each eye was stimula ed separately the other eye carefully co ered by an e e the adequacy of the co er was verified by the absence of an ERG from the co ered eye r a eraged ERG was then recorded with stimulat on by 32 flashes at 2 Hz frequency nultaneous sagittal VER was recorded Reverse pattern st mulator (D gitimer D 110) ed for subsequent VER exam nations The pat ent sat facing a translucent screen, d ng 33 at the eye onto wh ch the sl de of a black and wh te checkerboard was rojected The nd vidual squares subtended 60 at the eye The record ngs were made ating each e e separately the pat ent being asked to fixate a small red spot n the centre screen while the responses were be ng a eraged Pattern re ersal was produced once *cond by a rap d displacement of the checkerboard through one squa e The o erall* an e of the field d d not change The l ghts were off in the exam nation room but the ted l ght kept the room weakly llum nated The a erage response to 256 reversals was ced In 17 patients also half f eld st mulation was used The a eraging time was 200 nd

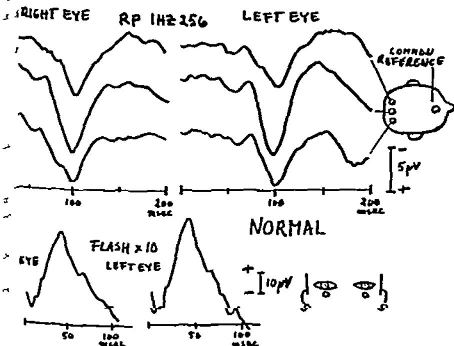


Fig 1

corneal ERGs w h s mulation b 10 flashes at 15-second n ervals and mid-occip tal and sagittal VERs w h st mulation b 256 pattern re ersals at 1 Hz frequency n one normal subject

ERGs were recorded from infraorbital skin electrodes with the ipsilateral [illegible] reference and the usual EEG electrodes at the vertex as the ground one. [illegible] disc electrodes 10 mm in diameter were attached by an adhesive ring to the [illegible] the centre of the pupil close to the lid margin and the contact was confirmed [illegible] paste VERs were recorded from three occipital electrodes all referred to a electrode 12 cm above the nasion The mid-occipital electrode for sagittal VER was [illegible] cm above the inion and parasagittal VERs were recorded from electrodes 5 cm to [illegible] left from the mid-occipital one

The primary amplification and recording of both ERG and VER was per[illegible] 16-channel Elema Siemens EEG-machine (Mingograph Universal) time constant [illegible] high frequency cut 70 Hz From the Mingograph the amplified signals were tra[illegible] 2-channel 1000 points signal analyser averager (Hewlett Packard 5480). The [illegible] responses were documented by means of Polaroid photographs from the [illegible] oscilloscope of the signal averager (Fig 1)

Table I

ERG The latencies (measured from the stimulus-on) and the amplitudes of b-[illegible] (measured from the trough of a waves) recorded from lower lid skin electrodes in [illegible] subjects (43 eyes) and in 26 patients with optic disc drusen (48 eyes) with stimul[illegible] flashes at 15 second intervals Same parameters in 15 of normal subjects (29 [illegible] patients with optic disc drusen (48 eyes) with stimulation by 32 flashes at 9 Hz [illegible]

	Normal		Optic disc drusen	
	Latency (msec)	Amplitude (µV)	Latency (msec)	Amplitude [illegible]
	b-wave	b-wave	b-wave	b-wave
	10 flashes at 15 second intervals (0 9 joule)			
	Mean SD n	Mean SD n	Mean SD n	Mean [illegible]
Right eye	39 8 ± 2 76 (22)	31 5 ± 13 22(22)	39 7 ± 4 69 ([illegible]3)	40 9 [illegible]
Left eye	39 6 ± 3 21 (21)	33 7 ± 13 40(21)	39 [illegible] ± 4 28 ([illegible]5)	[illegible]
Average R& L eye	39 7 ± 2 99 (43)	32 6 ± 13 31(43)	39 4 ± 4 44 ([illegible])	[illegible]
	32 flashes at 9 Hz frequency (0 2 joule)			
Right eye	39 6 ± 2 71 (15)	24 0 ± 11 89(15)	40 3 ± 3 60 ([illegible]3)	31 1 [illegible]
Left eye	39 8 ± 2 19 (14)	25 8 ± 14 67(14)	40 0 ± 4 10 ([illegible]5)	[illegible]
Average R& L eye	39 7 ± 2 45 (29)	24 9 ± 13 [illegible]8(29)	40 1 ± 3 8[illegible] ([illegible])	[illegible]

21

Results

patients with optic disc drusen showed from both eyes non-corneal ERGs ormal latency and normal amplitude of the b-wave the latency measured he stimulus-on and the amplitude from the trough of the a wave (Table I) tency and amplitude of the a wave were also in normal range

peak latency of the major positive wave of pattern VER from the mid 3 al and parasagittal electrodes and the peak to-peak amplitude of the major e wave measured to the immediately following negative peak were deter – The results were compared with those from 21 normal subjects The ude of the major positive peak was more variable than the latency also in l subjects The upper limit of normal for the latency of the peak of the major e potential in the pattern VER was considered to be the mean + 3 SDs which bout 111 mseconds

Table II

The latencies (measured from the pattern reversal) and the amplitudes of the major e component of VER (measured to the immediately following negative peak) recorded nid-occip tal electrodes in 21 normal subjects (41 eyes) and in 24 patients with optic disc 1 (42 eyes) with stimulation by 256 pattern reversals at 1 Hz frequency Some results parasagittal electrodes are also presented The fellow-eye in unilateral drusen was not included to the numbers

	Normal		Optic disc drusen	
	Largest positive wave		Largest positive wave	
	256 pattern reversals at 1 Hz frequency			
	Latency (msec)	Amplitude (µV)	Latency (msec)	Amplitude (µV)
	Mean SD n	Mean SD n	Mean SD n	Mean SD n
ccipital elect ode				
t eye	99 3 + 4 20 (21)	10 8 ± 5 54 (21)	98 7 ± 9 98 (20)	6 8 ± 3 84 (20)
eye	98 6 ± 3 76 (20)	11 1 ± 5 86 (20)	100 1 ± 15 71 (22)	5 4 ± 3 34 (22)
L eye	99 0 ± 3 98 (41)	11 0 ± 5 70 (41)	99 4 + 12 85 (42)	6 1 ± 3 59 (4)
agittal electrode				
eye to ateral e	99 6 ± 6 35 (37)	6 7 ± 3 69 (34)	98 5 ± 13 98 (49)	5 0 ± 2 39 (41)
eye to ralateral e	102 2 ± 5 69 (33)	7 5 ± 4 01 (37)	98 9 ± 12 30 (43)	5 3 ± 3 65 (43)

The whole group of 26 patients with optic disc drusen was so hete[illegible] the direct comparing of their VERs with those in normal subjects (Table [illegible]) reveals that the mean latency was the same as in normals but with l[illegible] deviation and that the mean amplitude was lower than in normals [illegible] difference was not significant because of the great interindividual [illegible] amplitudes also in normal subjects The amplitude of the major positive peak [illegible] from 3 1 µV to 26 2 µV in normals but under 5 µV it was only in three [illegible] eyes) whereas the variation in patients with optic disc drusen was from [illegible] 15 3 µV and in 13 patients (20 eyes) the amplitude was under 5 µV The [illegible] of the response was altered in eight cases with optic disc drusen

Seven different subgroups of patients with optic disc drusen are separately [illegible] visual fields were registered with both Goldmann and Friedmann methods.

1 Two patients had unilateral optic disc drusen with normal visual acuity in b[illegible] a slight visual field defect with an enlarged blind spot in the left eye with optic [illegible] The latencies of the major positive peak were normal but amplitudes were low [illegible] (3 6 µV and 3 1 µV 3 6 µV and 2 7 µV in the right and left eye respectively).

2 Two patients had unilateral optic disc drusen with decreased visual acuity [illegible] field defect in that eye The first patient with drusen in her right optic disc [illegible] chorioretinal scars near the macula causing decreased vision and small paracentral [illegible] in the visual field VER amplitudes were low in both eyes (4 3 µV and 4 6 µV in the [illegible] left eye respectively) and the latencies were normal with no difference between the [illegible] The second patient with drusen in his left optic disc had ten years previously experienced sudden decrease of vision with a temporal field cut in that eye Afterwards an [illegible] defect also developed and the optic disc became pale VER latency was [illegible] mseconds) in that eye and amplitude was lower than in the right eye (9 8 µV and [illegible]) [illegible] measurable VER was got with left half field stimulation of that eye The other eye [illegible] normal results also with half field stimulation

3 Three of the patients with bilateral optic disc drusen had normal visual a[illegible] normal visual fields in both eyes VERs showed normal latencies amplitudes and [illegible]

4 Five patients with bilateral optic disc drusen and normal visual acuity in b[illegible] showed unilateral minor visual field defects However no significant difference be[illegible] right and the left eye could be found in VER curves Two patients revealed broad [illegible] major positive waves and low amplitudes in both eyes the VERs of the others [illegible] also to half field stimulation

5 Ten patients had bilateral optic disc drusen with normal visual acuity but [illegible] field defects in both eyes Amplitudes could be low although the field defects were [illegible] four patients the amplitudes were under 3 µV in both eyes Latencies of the [illegible] wave were in normal range in all eyes and no significant difference between the [illegible] eye could be found although the visual field defects could be rather different in the [illegible] (Fig 2) The waveform of the major positive wave was broad in many cases and [illegible] to two peaks Half field stimulation used in seven patients gave better [illegible] ipsilateral parasagittal electrode as it did in normals without any correlation [illegible] the visual field defect that left the most central field intact.

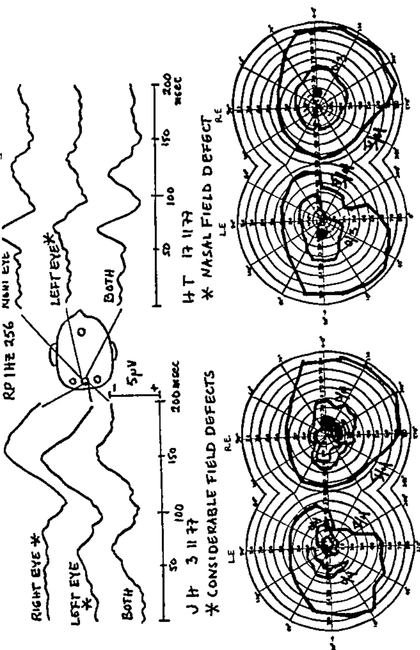


Fig –
Focipital VERs with stimulation by 9 6 pattern reversals at 1 Hz frequency in two patients with bilateral optic disc drusen and visual field defects

6 In two patients with bilateral optic disc drusen the visual acuity was decreas[illegible] eye One had amblyopia ex anopsia from uncorrected hyperopia and [illegible] but also a considerable nasal field defect The latencies of the major positive wave [illegible] longer in both eyes than in normals more so in the left amblyopic eye [illegible] (111 mseconds in the right and 124 mseconds in the left eye) The other [illegible] considerable visual field defect in the eye with decreased vision and also [illegible] that eye but VERs were in normal range in both eyes

7 The last small subgroup included two patients with bilateral optic disc [illegible] bilaterally decreased visual acuity One patient was examined four years after op[illegible] radiation of pituitary adenoma Before operation he had bitemporal field defects improved after therapy (Mustonen 1977) Major positive peaks were delayed [illegible] (129 mseconds in the right and 130 mseconds in the left eye) with some tendency [illegible] asymmetry from parasagittal electrodes typical for bitemporal hemianopia [illegible] compression (Blumhardt et al 1977) The other patient with bilateral optic disc [illegible] decreased vision in both eyes showed delayed major positive peaks in both eyes [illegible] mseconds in the right and 121 mseconds in the left eye) and amplitudes were [illegible] experienced difficulties with colour vision since childhood when he could not [illegible] blueberries or yellow cloudberries but could well discern red whortleberries [illegible] leaves Now he showed grave colour vision defects and visual fields revealed [illegible] scotomas Optic discs were rather pale with nasally situated drusen and [illegible] somewhat accentuated Foveal reflexes were absent and maculae were dark and [illegible] Dark adaptation revealed a cone plateau of very short duration but final [illegible] normal as well as ERGs after dark adaptation Fluorescein angiography showed [illegible] rescence in the area of pigment epithelium disturbance at both maculae He [illegible] have progressive cone dystrophy Family history revealed no other similar case

Discussion

Straub (1961) reported normal ERGs in patients with optic disc drusen [illegible] ERGs were found by Elenius et al (1961) in a case of tapetoretinal degen[illegible] combined with drusen of the optic discs and glaucoma simplex [illegible] (1958) reported subnormal or normal ERGs in three slightly night-blind [illegible] with optic disc drusen In the same family these authors also found absence [illegible] in two other siblings with fundus changes typical of retinitis punctata albe[illegible] optic disc drusen Ayesh et al (1976) presented a case with optic disc [illegible] retinitis pigmentosa and retinal teleangiectasia (Coats's disease) Both the [illegible] and photopic ERGs were almost totally extinguished In our 26 patients [illegible] disc drusen non-corneal ERGs were normal but the material did not [illegible] three patients with retinitis pigmentosa and two patients with [illegible] juvenile retinoschisis and optic disc drusen Babel et al (19[illegible]) in their [illegible] Electrophysiology described one patient with optic disc drusen whose EOG [illegible] normal and VERs of normal latency but with a split major positive wave [illegible]

3urvenich (1977) mentioned absolutely normal flash VER and PVER in a it with optic disc drusen and a slight enlargement of the blind spot Our series patients with optic disc drusen showed that in half of the cases VER was utely normal and in another half the amplitudes were rather low resulting in ower mean amplitude than in normal subjects but the interindividual variation o great also in normals that the difference was not significant. The waveform ie major positive peak was quite often broad or split (eight cases of all) ncies were usually in normal range although the visual field defects could be severe Therefore some other cause should be thought if the latency of the r positive peak in pattern VER is delayed in patients with optic disc drusen

References

man P Chadwick D W & Marsden C D (1975) Visual evoked responses in the gnosis and management of patients suspected of multiple sclerosis Brain 98 261–282

h I Sanders M D & Friedmann A I (1976) Retinitis pigmentosa and Coats s disease t J Ophthal 60 7 5–777

I J Stangos N Korol S & Spiritus M (1977) Ocular Electrophysiology A Clinical and perimental Study of Electroretinogram Electro-oculogram Visual Evoked Response p 3 Thieme Stuttgart

:tt G Blumhardt L Halliday A M Halliday E & Kriss A (19 6) A paradox in the :ralisation of the visual evoked response Nature 261 253–255

G (1978) Das Elektroretinogram und das evozierte Sehrindenpotential bei normalen d an Glaukom erkrankten Augen Albrecht v G aefes Arch klin exp Ophthal 20 3–269

hardt L D Barrett G & Halliday A M (1977) The asymmetrical visual evoked tential to pattern reversal in one half field and its sign f cance for the analysis of visual ld defects Brit J Ophthal 61 454–461

stein Y (19 5) The pattern evoked response (VER) in optic neuritis Albrecht G aefes ch kl n exp Ophthal 197 101–106

e H Olsson J E & Rosen I (1977) Diagnostic value of visual evoked response clinical examination and CSF analysis in chronic myelopathy Acta Neu ol Scand 56 55–69

on J M & Nissim S (1975) Visual e oked responses in the assessment of f eld defects in ucoma A ch Ophthal (Chicago) 93 9–18

sia G G & Daly R F (1977) Visual electroencephalograph c computer analysis (VECA) new electrophysiologic test for the diagnosis of optic nerve lesions Neu ol gy 27 7–641

n F Mallecourt J Leblanc M & Lhermitte F (1977) Apport de l enregistrement des tentuels evoques visuels au diagnostic de la sclerose en plaques Rev Neu l 133 81–88

ius V Forsius H & Eriksson A W (1961) Subnormal electroretinograms in a case of etoretinal degeneration combined with drusen of the optic disc and glaucoma simplex ta Ophthal (Kbh.) 39 343–351

iberger C Jr & Ziegler S B (19 7) Visual evoked potentials and quantitati e perimetry multiple sclerosis Ann N u ol I 561–564

Erkkila H (1977) Optic disc drusen in children *Acta ophthal (Kbh) 5 ...*
Feinsod M & Hoyt W F (1975) Subclinical optic neuropathy in multiple sle... VER components reflect axon loss and conduction defects in optic pa... *Neurosurg Psychiatry 38* 1109–1114
Fotzsch R Fruhauf A & Fabricius E M (1978) Zur Klinik der Drusenpapi... *3* 12–17
Halliday A M McDonald W I & Mushin J (1972) Delayed visual evoked resp... neuritis *Lancet I* 982–985
Halliday A M McDonald W I & Mushin J (1973) Visual evoked response in multiple sclerosis *Brit Med J 4* 661–664
Halliday A M Halliday E Kriss A McDonald W I & Mushin J (19..) The p... potential in compression of the anterior visual pathways *Brain 99* ...
Hennerici M Wenzel D & Freund H J (1977) The comparison of small-size ... checkerboard stimulation for the evaluation of delayed visual evoked respon... suspected of multiple sclerosis *Brain 100* 119–136
Hoeppner T & Lolas F (1978) Visual evoked responses and visual sympto... sclerosis *J Neurol Neurosurg Psychiatry 41* 493–498
Lansche R K & Rucker C W (1957) Progression of defects in visual fields ... hyaline bodies in optic disks *Arch Ophthal (Chicago) 55* 115–1[..]
Lorentzen S E (1966) Drusen of the optic disk A clinical and genetic study *(Kbh) Suppl 90* 1–180
Lowitzsch K Kuhnt U Sakmann Ch Maurer K Hopf H C Schott D & Th... Visual pattern evoked responses and blink reflexes in assessment of MS ... clinical study of 135 multiple sclerosis patients *J Neurol 213* 1...–3
Mastaglia F L Black J L Cala L A & Collins D W K (19..) Evoked poten... velocities and computerised tomography in diagnosis of multiple sclerosis ... 1315–1317
Milner B A Regan D & Heron J R (1974) Differential diagnosis of multiple ... visual evoked potential recording *Brain 97* 755–772
Mustonen E (1977) Optic disc drusen and tumours of the chiasmal region ... *55* 191–200
Mustonen E & Sulg I (1980) Electroretinography by skin electrodes and ... method *Acta ophthal (Kbh) 58* 388–396
Namerow N S & Enns N (1972) Visual evoked responses in patients with ... *J Neurol Neurosurg Psychiatry 35* 829–833
Neetens A & Burvenich H (1977) Autofluorescence of optic disc-drusen ... *Ophthal 1*[..]*9* 103–110
Nikoskelainen E Sogg R L Rosenthal A R Friberg T R & Dorfman L J ... early phase in Leber hereditary optic atrophy *Arch Ophthal (Chicago) 95* ...
Pats J Brenot P Henry P & Faure J M A (19.6) Potentiels evoques visuels ... plaques *Rev Neurol 132* 605–621
Pietruschka C & Priess G (1973) Zur klinischen Bedeutung und Prognose der D... *Klin Mbl Augenheilk 162* 331–341
Regan D Milner B A & Heron J R (19 6) Delayed visual perception and ... evoked potentials in the spinal form of multiple sclerosis and in retrobulbar n... *99* 43–66
Richey E T Kooi K A & Tourtellotte W W (1971) Visually evoked respons... sclerosis *J Neurol Neu...urg Psychiatry 34* 275–...80

berg M A Savino P J & Glaser J S (1979) A clinical analysis of pseudopapilledema opulation laterality acuity refractive error ophthalmoscopic characteristics and cident disease *Arch Ophthal (Chicago) 97* 65–70
r C W & Kearns T P (1961) Mistaken diagnosis in some cases of meningioma *Amer J thal 51* 15–19
) P J Glaser J S & Rosenberg M A (1979) A clinical analysis of pseudopapilledema visual field defects *Arch Ophthal (Chicago) 97* 71–75
okhi F Chiappa K H & Young R R (1978) Pattern shift visual evoked responses o hundred patients with optic neuritis and/or multiple sclerosis *Arch Neurol 35* 65–71
b W (1961) Einige Erkrankungen des Sehnerven in elektroretinographischer Sicht *on Res 1* 920–927
as S & Setala M (1958) On atypical night blindness *Acta ophthal (Kbh) 36* 849–859
berger H (19 6) Retrobulbarneuritis und visuell evozierte Potentiale *Kl n Mbl Augen k 168* 98–100
J A (1977) Pattern visual evoked responses in multiple sclerosis *A ch Neu ol 34* 4–316

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Mustonen M D *Department of Ophthalmology*
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Erkkila H (1977) Optic disc drusen in children *Acta ophthal (Kbh) Suppl 129*
Feinsod M & Hoyt W F (1975) Subclinical optic neuropathy in multiple sclerosis VER components reflect axon loss and conduction defects in optic pathways *Neurosurg Psychiatry 38* 1109–1114
Fotzsch R Fruhauf A & Fabricius E M (1978) Zur Klinik der Drusenpapille
3 12–17
Halliday A M McDonald W I & Mushin J (1972) Delayed visual evoked response in optic neuritis *Lancet I* 982–985
Halliday A M McDonald W I & Mushin J (1973) Visual evoked response in diagnosis of multiple sclerosis *Brit Med J 4* 661–664
Halliday A M Halliday E Kriss A McDonald W I & Mushin J (1976) The pattern evoked potential in compression of the anterior visual pathways *Brain 99*
Hennerici M Wenzel D & Freund H J (1977) The comparison of small-size rectangle and checkerboard stimulation for the evaluation of delayed visual evoked responses in patients suspected of multiple sclerosis *Brain 100* 119–136
Hoeppner T & Lolas F (1978) Visual evoked responses and visual symptoms in multiple sclerosis *J Neurol Neurosurg Psychiatry 41* 493–498
Lansche R K & Rucker C W (1957) Progression of defects in visual fields produced by hyaline bodies in optic disks *Arch Ophthal (Chicago) 58* 115–121
Lorentzen S E (1966) Drusen of the optic disk A clinical and genetic study *Acta ophthal (Kbh) Suppl 90* 1–180
Lowitzsch K Kuhnt U Sakmann Ch Maurer K Hopf H C Schott D & Thater K Visual pattern evoked responses and blink reflexes in assessment of MS diagnosis clinical study of 135 multiple sclerosis patients *J Neurol 213* 17–32
Mastaglia F L Black J L Cala L A & Collins D W K (1977) Evoked potentials velocities and computerised tomography in diagnosis of multiple sclerosis *Brit*
1315–1317
Milner B A Regan D & Heron J R (1974) Differential diagnosis of multiple sclerosis visual evoked potential recording *Brain 97* 755–772
Mustonen E (1977) Optic disc drusen and tumours of the chiasmal region *Acta*
55 191–200
Mustonen E & Sulg I (1980) Electroretinography by skin electrodes and signal averaging method *Acta ophthal (Kbh) 58* 388–396
Namerow N S & Enns N (1972) Visual evoked responses in patients with
J Neurol Neurosurg Psychiatry 35 829–833
Neetens A & Burvenich H (1977) Autofluorescence of optic disc-drusen
Ophthal 179 103–110
Nikoskelainen E Sogg R L Rosenthal A R Friberg T R & Dorfman L J early phase in Leber hereditary optic atrophy *Arch Ophthal (Chicago)*
Paty J Brenot P Henry P & Faure J M A (1976) Potentiels evoques visuels et plaques *Rev Neurol 132* 605–621
Pietruschka C & Priess G (1973) Zur klinischen Bedeutung und Prognose der Drusen *Klin Mbl Augenheilk 162* 331–341
Regan D Milner B A & Heron J R (1976) Delayed visual perception and delayed evoked potentials in the spinal form of multiple sclerosis and in retrobulbar neuritis
99 43–66
Riches E T Kooi K A & Tourtellotte W W (1971) Visually evoked responses in sclerosis *J Neurol Neurosurg Psychiatry 34* 27 980

	Age at follow up	Crade of vital sta n ng	Cornea sl t lamp	Pachy e ry			End l elial cell den y		V on	
				Befo e pera on	La t exam tal stained	Co ntral eye pcs op last exam n n stained	V al sta ned eye	Co trulat n n sta ned eye la t exam	V tal sta ned eye	Co tral t non sta ned eye
1	C7 M	1	op city o u	0 48	0 48	0 45	1979	1C12	C C	<C C
9	C8 M	9	nat	0 54	0 51	0 50	1992	1860	C 9	6 6
3	69 M	2	nat	0 57	0 49	0 47	9 07	2C35	6 6	C 36
4	70 F	3	nat	0 50	0 50	0 51	219	9430	C 9	C J
5	72 F	2	na	0 3	0 53	0 6	1538	1240	<C C	<C 6
C	7C F	0	nat	0 53	0 50	0 9	034	2447	C C	C C
7	76 F	3	opacity o u	0 51	0 58	0 48	999	1C37	<C 94	C/18
8	78 M	2	nat	0 47	0 45	0 45	238J	24C8	C C	<C 6
J	78 F	0	nat	0 51	0 54	0 56	1881	900 J	>6 12	6 9
10	79 M	3	nat	0 48	C 51	1 10*	1649		C 9	1**
11	80 M	1	na	0 69	0 53	0 9	1 90	1 84	<C 12	C 9
19	82 F	1	nat	0 45	0 44	0 49	19J9	1438	C 24	C 9
13	8 F	2	na	0 49	0 1	0 53	137	1393	C 12	C J
14	90 F	0	nat	0 51	0 J0	0 48	93J7	2117	1 C0	1 C0
15	9 F	2	nat	0 53	0 4J	0 49	23J5	9 J J	C C0	<C 19
mean ± EM				0 59 ±0 01	0 50 +0 03	0 51 ±0 01	1839 ±11C	1344 +120		

* I rev ou ly opera ed on for glaucon a ** Pt s s bulb

Table II

Aphakic eye vital stained by trypan blue compared with contralateral non-operated control eye. Eight patients examined by scleral scatter, pachymetry and endothelial cell count

	Age at follow up	Grade of vital staining	Cornea slit lamp	Pachymetry			Endothelial cell density		Vision
				Before operation	Last exam vital stained	Contralat. eye last exam non stained	Vital stained eye	Contralat. non stained eye last exam	Vital stained eye
1	63 F	4	opacity o.u.	0.48	0.78	0.4[illegible]	–	–	1/36*
2	[illegible] 3 F	3	nat	0.[illegible]	0.[illegible]0	0.53	[illegible]18	[illegible]30	6/9
3	[illegible]3 M	[illegible]	nat	0.[illegible]	0.5[illegible]	0.5[illegible]	2811	932	6/6
4	71 M	1	nat	0.42	0.4	0.[illegible]6	1138	–	[illegible]
5	82 F	3	nat	0.50	0.47	0.4[illegible]	[illegible]	–	[illegible]/24*
6	81 F	2	nat	0.[illegible]	0.[illegible]	0.[illegible]	16[illegible]	[illegible]098	>1/60
7	87 F	1	band shaped keratopathy	0.47	0.[illegible]	0.[illegible]7	[illegible]	–	[illegible]
8	[illegible]	0	[illegible]	0.[illegible]	0.48	0.48	[illegible]	[illegible]	[illegible]

Table III

oman aged 61 Vital staining by trypan blue during cataract extraction o u onounced senile macular degeneration of the retina and sequels of acute glaucoma in both eyes

Grade of vital staining	Cornea slit lamp	Pachymetry		Endothelial cell density	Vision
		initially	last exam		
1	nat	0 46	0 52	1°56	1 60
3	nat	0 59	0 50	137°	H + P

Material

)perative vital staining was performed on 47 patients subjected to cataract iction (Norn 1971) These were followed up 6 to 12 months later (Norn 1973) ie time of the present investigation eight years after the operation 22 had died one had emigrated (address unknown) The remaining 24 (51% of the series) been summoned and all appeared for examination Age at follow up and sex hown in Tables I II and III

fteen had both eyes operated on for cataract The one eye had been vital ied while the contralateral eye acted as an aphakic control eye (Table I) Eight only one eye operated on and vital stained during operation (Table III)

Methods

trypan blue was an aqueous solution for intravenous use having no salts added isotonicity nor buffer

he procedure of cataract extraction has been described previously (Norn 1971) ha-chymotrypsin was employed for all aged under 60 a total of five trypanblue ned eyes

In the eight year follow up the cornea was examined in the slit lamp in ticular for cloudiness Using scleral scatter technique the eyes were examined corneal oedema (Norn 1974)

he central thickness of the cornea was measured by means of Haag Streit s hymeter and Kaufmann s specular endothelium microscope (Knight et al 78)

The number of endothelial cells centrally on the cornea was calculated on the is of the best three photographs out of about nine takings per eye using

Kaufmann s contact endothelium microscope Sperling s method was ... the counting to avoid counting each cell more than once (Sperling et al ...

Results

The results are shown in Tables I–III The *cornea* showed no oedema ... examination Corneal opacity was observed in only four of the vital-stain... six of the control eyes These corneal opacities were seen in patients oper... glaucoma (two + two control eyes) band shaped calcareous keratopathy ... control eye) metaherpetic keratopathy (one control eye) phthisis (one co... and opacity over the area of the operation scar (one + one control eye)

A *visual acuity* of 6/12 of better (≧ 20/40) was obtained in 13 out of 2... aphakic eyes The visual impairment of the remaining 12 eyes was du... macular degeneration (n = 8) or – though rarely keratopathy before (three) or stabismic amblyopia (one)

The *corneal thickness* averaged 0 52 mm prior to the cataract ext... control eight years later the thickness was unchanged assessed by the Haag Streit pachymeter It did not differ significantly from the c... operated eye (Table I) nor from the non-operated eye (Table II)

Neither did specular microscopy reveal any significant differences.

There was no difference in *central corneal endothelial cell density* b... vital stained eye and the corresponding aphakic control eye (Table II... was of cause reduced after cataract extraction (Table II)

The coefficient of variability of the first two measurable duplicate ... was 12% (n = 36 out of 42)

The grade of trypan blue vital staining of the endothelium peropera... use of alpha-chymotrypsin do not seem to influence the parameters stud...

Panophthalmia or marked iritis were not seen in the observation perio...

Comments

Vital staining seemed not to be the cause of endothelial cell damage as ... cell counting and pachymetry

The endothelial cell count was found to have a high coefficient of ... presumably because a number of the old patients were unable to ... sufficiently The above mentioned conclusion must therefore be taken ... reservation

References

P M Link W J & Kaufman H E (19 8) *The corneal endothelium.* A review of ure Heyer Schulte Medical Optics Center Irvine Ca U S A
S (1971) *vital staining of corneal endothelium in cataract extraction Acta ophthal.* *49* 725–753
I S (1973) Pachometric study of the influence of corneal endothelium vital staining *phthal. (Kbh) 51* 679–686
I S (1974) External Eye Methods of Examination p 200 Scriptor Copenhagen
homas (1979) Non-contact specular microscopy of human corneal endothelium *Acta al. (Kbh.) 57* 986–998
g S & Gunderson H J (1978) The precision of unbiased estimates of numerical ty of endothelial cells in donor corneas *Acta ophthal (Kbh.) 56* 793–802

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PAS POSITIVE POLYMORPHONUCLEAR LEUCOCYTES IN CORNEAL ULCERS

BY

J. U. PRAUSE and O. A. JENSEN

Fifty consecutive cases of severe keratitis with clinical signs of corneal [illegible] were examined histologically for the stage of inflammatory reaction. [illegible] 14 similar cases were studied ultrastructurally.
Cell counts of polymorphonuclears (PML), eosinophils, lymphocytes and plasma cells were carried out. Further the corneas were grouped according to their content of PAS positive PML. The state of ulceration was [illegible] microscopically.
PML at a cell count of > 10 cells mean field (× 1000) were found in [illegible] cases and were significantly more frequent in corneal areas with epithelial [illegible] Descemet membrane defects. Most PML were PAS-positive [illegible] positive material having the characteristics of glycogen. PAS-negative P[illegible] were found in corneas with increased amount of plasma cells.
By TEM the PML were found highly phagocytic, partly degranulated and [illegible] reduced glycogen content. TEM could not, on the formalin fixed specimens, determine whether PAS negative PML had a higher protein turnover [illegible] findings indicate that corneal ulcers with PAS-negative PML contain a [illegible] amount of proteases, because of many degranulated PML and probably [illegible] reactivation of PML. Therefore the PAS stainability can be used as an [illegible] for the PML activity in corneal ulcers.

Key words: corneal ulcer – polymorphonuclear leucocytes – [illegible] granulocytes – lymphocytes – plasma cells – PAS-staining – tissue turnover [illegible]

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as been published concerning the stainability of the neutrophilic polymor lear leucocytes (PML) in histological sections of inflamed corneas As the of PAS-positive PML in corneal lesions was observed to vary the aim of the study was to determine the material which was responsible for the PAS 1 and to reveal any relationship between the presence in the cornea of sitive PML and the severity of the corneal lesion

Material and Methods

it microscopical part of the study comprised 50 consecutive cases of severe keratitis linical diagnosis of corneal ulcers referred to the Eye Pathology Institute (1970– The material consisted of 28 males and 22 females The median age of patients was 74 ange of 5–99 years The preceding history of corneal disease had a median duration ys (range 3 – approx 300) The aetiology of the cases is stated in Table I

es had been fixed in 10% buffered neutral formalin for 24 h processed according to *paraffin technique and cut in 8 μm sections*

raffinized hydrated sections were digested for 1 h at 37°C with 0 5% hog pancreas se (type VI A M lot 76C 0096 Sigma St Louis) in 0 5 M phosphate buffer pH 6 5 yme concentration used in this study was determined in a pilot study with a dilution f α amylase (5→0 05%) Neighbouring control sections were treated with phosphate lone

ctions were stained with periodic acid Schiff a m McManus (PAS) Some PAS-stained were digested and re stained

ity five sections from each patient were examined by light microscopy (LM) (900×) ects in the corneal layers recorded Defects in the epithelium were only counted when sections showed a total loss of epithelium in the ulcer area. Defects in the endothel um t recorded as they were often due to trauma caused by the technical procedure

Table I
Aetiology of corneal ulcers

Aetiology	Number
Posttraumatic	4
Following cataract extraction	6
Graft rejection	4
Exposure keratitis	5
Bacterial infection	5
Viral infections (Herpes simplex)	10
Other	16
Total	50

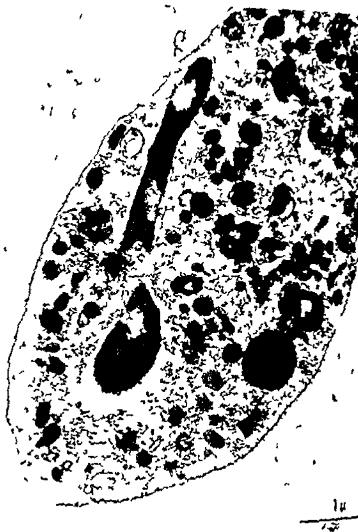


Fig 3
Electron micrograph of PAS-positive PML showing dispersed glycogen (C) [illegible] and several phagosomes (P) (Lab No 367/78 TEM 3x9 × [illegible])

PML were significantly more frequent ($P < 0.05$) in sections with epithe[illegible] or defects in Descemet's membrane PAS negative PML were found [illegible] plasma cells but there were no differences between the groups [illegible] relation to the other examined parametres

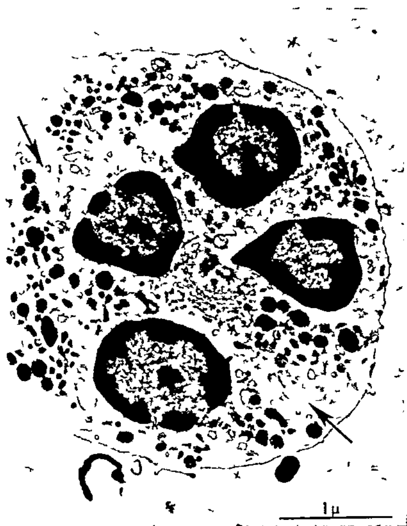


Fig. 4
digested specimen showing PML with loss of cytoplasmic glycogen lea ing clear cytoplasmic areas (arrows) (Lab No 9?2 78 TEM 346 ×28 500)

amination The PML were naturally not so well preserved as in tissue ly processed for TEM However the nucleus and cytoplasm were quite well ed the plasma membrane being sometimes destroyed The PAS-positive owed in the cytoplasm abundant dispersed β-particles of glycogen digestable



Fig 5
PML in liquefied part of ulcer with only a few granules sparse gl rgra phagosomes (P) containing material of same morphology as the surrounding collagen (C) (Lab No 793/79 TEM 436 x 16 800)

by α amylase (Figs 3 4) In addition these PML showed several ph various sizes They contained a granular material of the same structu degraded collagen surrounding the cells (Figs 3 5) In less destroyed corneal stroma macrophages with phagocytosed PML were found (Fig 6)

Discussion

¬ et al (1979) found granulocytes containing PAS-positive material ler this was amylase resistant in contrast to our PAS-positive material

usual histological paraffin technique has been considered as removing en This however is not the case (Paegle 1965 Poulsen 1979) Glycogen is d by amylases and it is therefore very probable that the α amylase sensitive ial observed in the PML was glycogen Furthermore pilot studies using ent concentrations of α amylase ensured that the enzyme concentration yed was sufficient to exclude any false amylase reaction

TEM the presence of glycogen in PAS-positive PML was established The gen was seen as β-particles digestable by amylase

e prometamyelocytes have only little glycogen (Staples & Getaz 1977) and are n azurophil granules containing most of the tissue degrading enzymes such as se hyaluronidase cathepsin G and collagenolytic serine protease (Rowsey et 75 Keiser et al 1976 Starkey & Barret 1976 Ohlsson et al 1977)

cogen particles accumulate in metamyelocytes and increase with maturation increase in glycogen content is followed by an increase in number of specific iles (Bainton et al 1971) containing collagenase (Baggioline 1979) At the time the number of azurophil granules is reduced

st glycogen is found in the mature circulating PML which contain a limited ber of granules These PML represent the non-dividing non-secretory end of the cells (Staples & Getaz 1977) Since the PAS-positive PML are end stage with limited protease content, the tissue destructive capacity in a corneal ulcer uted to the number of PML present, and if a replenish with PML is prevented egantly shown by Kenyon et al (1979) the destructive capacity therefore is ed Our findings confirm on a human material, the experimental findings of on et al. (1979) especially the presence of the phagocytic active partly anulated PML with a variable content of glycogen found in the melting areas e ulcer We also found macrophages containing PML remnants in the more pheral parts of the ulcer (Fig 6)

e PAS-negative PML were found together with plasma cells and by TEM they often found in melting areas of the cornea

e PAS-negative PML contained many phagolysosomes sign[illegible] teases Unfortunately our routine formalin fixed specimens do not allow a nutative TEM examination of the Golgi apparatus and endoplasmatic reti um It is therefore impossible to decide whether the PAS-negative PML are ner PAS-positive PML which have degranulated and at the same time have used r glycogen content and are now dying However it could also be PML which are tivated to a prometamyelocytic stage rebuilding their granules i.e reactivated

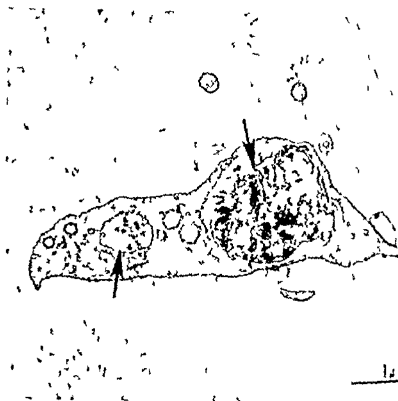


Fig 6
Area in non liquefied part of ulcerated cornea with macrophage having [illegible] (arrows) The cell is surrounded by regularly arranged collagen fibres (Lab [illegible] TEM 3?9 × ?8 ?00)

like lymphocytes The PAS negative PML are not genuine prometa[illegible] they contain mature lobulated nuclei

The presence of plasma cells together with PAS-negative PML a[illegible] interest because when PML is phagocytosing immune complexes [illegible] enzymes are released (Movat 1979)

Thus a corneal ulcer with a high amount of PAS-negative PML [illegible] increased liberation of tissue destroying proteases as found in [illegible] corneal ulcers

Our findings may therefore support PML proteases responsible for the stromal liquefaction found in immunological active corneal ulcers ([illegible] 1978) and the high collagenolytic activity found in corneal tissue [illegible] PML (Pirie et al 197?)

The present study was not designed to take account of the medical [illegible]

before enucleation — and the use of various antibiotics or particularly of corticosteroids factors which might be of importance to our findings
study also confirms earlier findings that PML mainly accumulate in denuded of the cornea (Haik & Zimmy 1977 Sheppard et al 1971) which indicates part of the PML are brought to the ulcer by the tear fluid (Wine & Basu 1958 & Kuwabara 1962)

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References

lint M (1979) Inflammatory phagocytes Their properties and their involvement in matoid arthritis *Triangle 18* 53–61
w D F Elliot J L & Farquhar M G (1971) The development of neutrophilic morphonuclear leukocytes in human bone marrow *J Exp Med 134* 907–935
G & Zimmy M L (1977) Scanning electron microscopy of corneal wound healing in abbit *Invest Ophthal Vis Sci 16* 787–796
L D Rosen D D & Berk R S (1978) Murine corneal response to heat inactivated domonas aeruginosa *Ophthal Re 10* 73–81
H Greenwald R A Feinstein G & Janoff A (1976) Degradation of cartilage eoglycan by human leucocyte granule neutral proteases — A model of joint injury *J Invest 57* 625–632
n K R Berman M Rose J & Gage J (1979) Prevention of stromal ulceration in the l-burned rabbit cornea by glued-on contact lens Evidence for the role of polymor nuclear leucocytes in collagen degradation *Invest Ophthal Vis Sci 18* 5 0 587
H Z (1979) Tissue injury and inflammation induced by immune complexes The cal role of the neutroph l leukocyte *Exp m l path l 31* 901–910
n K Olsson I & Spitznagel J K (1977) Localization of chymotryps n like cationic ein collagenase and elastase in azurophil granules of human neutroph lic polymor nuclear leucokytes *Hoppe Seylers Z Phy ol Ch m 358* 361 366
R D (1965) *Factors affecting enzymatic removal of glycogen from tissue sections and entire rat liver blocs J Histochem Cytochem 13* 488 497
RT Eguchi M Spicer S S (1979) Ultrastructural cytochemistry of complex ohydrates in leucocyte granules *J Histochem Cytochem 27* 1167–1170
Werb Z & Burleigh M C (1975) Collagenase and other proteinases in the cornea of retinaldeficient rat *Brit J Nutr 34* 297 309
n H (19 8) Personal communication
R M & Kuwabara T (1962) Corneal wound heal ng *A ch Ophthal (Chicago) 68* –649
I Nisbeth M R Swedo J L & Katona L (19 6) Corneal collagenolytic activity in bit polymorphonuclear leukocytes *J Ultra Re 57* 10–21

Sheppard L. B. Shaurlin W. M. Harris T. M. & Fox R. R. (19 [illegible]) [illegible] regenerating epithelium of normal and buphthalmic rabbit cornea [illegible] 116–125
Staples W. C. & Getar E. P. (1977) The present status of cytochemistry in [illegible] haematological malignancy *S. A. Med J.* 4 838–841
Starkey P. M. & Barret A. J. (1976) Neutral proteinases of human spleen *[illegible]* 255–265
Wine N. A. & Basu P. K. (1958) Studies on corneal wound healing [illegible] *Amer J Ophthal* 46 253–258

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\CTERIAL FLORA IN RELATION TO CATARACT EXTRACTION

V Effects of Topical Antibiotics on the Preoperative Conjunctival Flora

BY

J A. FAHMY

In a randomized study comprising 60 patients six different prophylactic regimens were evaluated for their effectiveness in eradicating bacteria on the conjunctivas before surgery Gentamicin sulfate ophthalmic solution was the only antibiotic able to eliminate bacteria in almost all of the examined patients The other drugs (chloramphenicol solution oxytetracycline polymyxin B ointment, sulphamethizole bacitracin neomycin and ristocetin polymyxin B solutions) were not effective although most of the isolated strains were sensiti e to the respective antibiotics probably because of the short treatment period (18 h) The problem of prophylactic therapy n ophthalmology is discussed and some guide lines are given

Key words bacteria – conjunctiva – antibiotics – cataract extraction – endophthalmitis – prophylaxis

prophylactic role of topical antibiotics administered prior to intraocular ery is still the subject of dispute

veral authors (Dunnington & Locatcher Khorazo 1945 Callahan 1953 Locat r Khorazo 1953 Locatcher Khorazo & Gutierrez 1956 1972 Allen & Mangia ne 1964 1974) stated that the elimination reduction or suppression of genous ocular flora – the principal remaining hazard in intraocular surgery significantly reduce the occurrence of postoperative infection Others (Leo- d 1958 Leopold & Apt 1960 Goodner 1963 Leopold 1971 1972) disagreed l claimed that the surgical field in ophthalmology cannot be completely ilized and the use of topical antibiotics may lead to the alteration of the local

eived December 4 19 9

Table I
Age and sex distribution

Age	Sex		Total
	F	M	
≤ 50	2		[illegible]
51 60	5	2	7
61 70	14	8	[illegible]
71 80	11	4	15
≥80	3	11	14
Total	35	25	60

conjunctival flora permitting the development of pathogens which [illegible] because competitive organisms have been inhibited Further the [illegible] lactic therapy may allow one to develop or encourage the multiplication [illegible] strains

Although the subject is of much interest only insufficient data exist [illegible] time to determine the effect of short time usage of antibiotics on the [illegible] flora It has therefore been the main purpose of the present study to [illegible] this problem

Material and Methods

The material comprises 60 patients admitted to the Department of [illegible] logy Kommunehospitalet Copenhagen during the period [illegible] for cataract extraction The age and sex distribution can be seen from Table I

Only Cases without any signs of inflammation or infection were [illegible] Further it was made certain that none of them had received any [illegible] corticosteroids during the last months prior to operation

The patients received randomly one of the following drugs 1) [illegible] ophthalmic solution 0 5% 2) gentamicin sulphate ophthalmic [illegible] 3) oxytetracycline chloride 3% – polymyxin B sulphate 0 1% ophthalmic [illegible] 4) sulphamethizole ophthalmic solution 4% 5) bacitracin 1% – [illegible] 0 5% ophthalmic solution and 6) ristocetin sulphate 0 5% – polymyxin B [illegible] 0 25% ophthalmic solution Thus each treatment group included 10 [illegible] drug was applied 5 times starting shortly after admission (approximately [illegible] surgery) and ending at bed time

enal cultures were taken before the antibiotic treatment, and again the next
iortly before operation Methods of obtaining cultures identification of
ia and preparation for surgery were similar to those described elsewhere
et al 1975a b)

Results

imphenicol

Table II it may be seen that a total of 22 bacterial strains were isolated before
nent. Chloramphenicol was effective in the elimination of 10 strains while 12
s remained uninfluenced Six new strains were recovered after treatment
the sign test was applied this effect was found not significant ($P > 0\ 05$)
vity tests were performed and showed that six strains (all belonged to
iylococcus albus) out of 40 were resistant to chloramphenicol (22 isolates
e and 18 after treatment)

imicin

ffective in the elimination of 21 out of 22 isolated strains (Table III) One
S albus remained uninfluenced while no new stranins were recovered after
ment (sign test $P < 0\ 01$) None of the strains were resistant to gentamicin (total
ber of isolates is 23)

Table II

t of *chlo amphenicol* eye drops on bacterial strains isolated from 10 normal non infected eyes

icroorganisms	Treatment	Number of strains			
	Before	+ growth	+ growth	− growth	− growth
	After	+ growth	− growth	+ growth	− growth
albus		9	4	5	
orynebacteria			2		
aureus		9			
reptococcus non haemolyticus		1	9	1	
anitratum			1		
nidentified gram negative bacilli			1		

Table III

Effect of *gentamicin* eye drops on bacterial strains isolated from 10 normal eyes

Microorganisms	Treatment	Number of strains			
	Before	+ growth	+ growth	growth	r
	After	+ growth	− growth	+ growth	
S albus		1	11		
Corynebacteria			2		
S aureus			1		
Streptococcus non haemolyticus			9		
faecalis			1		
B anitratum			5		
Unidentified gram negative bacilli			1		

Oxytetracycline – polymyxin B

was ineffective against 11 out of 17 strains two new strains were recovered after treatment (sign test $P > 0\ 05$) (Table IV) Four strains S albus were resistant to oxytetracycline two S aureus to polymyxin B and one strain Proteus mirabilis to both antibiotics (total number of isolates is 30)

Table IV

Effect of *oxytetracycline polymyxin* eye ointment on bacterial strains isolated from non infected eyes

Microorganisms	Treatment	Number of strains			
	Before	+ growth	+ growth	− growth	r
	After	+ growth	− growth	+ growth	
S albus		9	2	1	
Corynebacteria			2	1	
S aureus		1			
P mirabilis		1			
E cloacae			1		
B anitratum			1		

Table V

of *sulphamethizole* eye drops on bacterial strains isolated from 10 normal non infected eyes

	Treatment	Number of strains			
oorganisms	Before	+ growth	+ growth	− growth	− growth
	After	+ growth	− growth	+ growth	− growth
ous		10	1	4	
nebacteria		1	2		
ireus			1		
ptococcus non haemolyticus			1	1	
nitratum				1	

iamethizole

neffective in the elimination of 11 out of 16 strains six new strains were ered after treatment (Table V) (sign test $P > 0\ 05$) Only one strain S albus esistant to sulphamethizole (total number of isolates is 33)

racin – neomycin

neffective in 12 out of 20 instances four strains were recovered after treatment

Table VI

t of *bacitracin neomycin* eye drops on bacterial strains isolated from 10 normal non infected eyes

	Treatment	Number of strains			
icroorganisms	Before	+ growth	+ growth	− growth	− growth
	After	+ growth	− growth	+ growth	− growth
albus		10	2	1	
orynebacteria		1	1	1	
aureus		1			
treptococcus non haemolyticus			3		
anitratum			1	1	
nidentified gram negative bacilli			1		

Table VII

Effect of ristocetin polymyxin B eye drops on bacterial strains isolated from infected eyes

Microorganisms	Treatment	Number of strains		
	Before	+ growth	+ growth	growth
	After	+ growth	− growth	+ growth
S albus		10	5	1
Corynebacteria			1	1
S aureus		1		
Streptococcus non haemolyticus			2	1
B anitratum			1	

(Table VI) (sign test $P > 0.05$) No sensitivity test was performed [illegible] (total number of isolates is 35)

Ristocetin – polymyxin B

Failed to eliminate 11 out of 19 strains three new strains were [illegible] treatment (Table VIII) (sign test $P > 0.05$) Three strains (two S albus [illegible] Streptoccoccus non haemolyticus) were resistant to polymyxin B and [illegible]

Table VIII

Effect of topical antibiotics on the conjunctival bacterial flora (total [illegible]) 60 patients

Antibiotics	Before treatment	+	+	[illegible]	
	After treatment	+	−	[illegible]	
Chloramphenicol		10	0	0	
Gentamicin		1	0	0	
Oxytetracycline polymyxin B		10	0	0	1
Sulphamethizole		10	0	0	
Bacitracin neomycin		1	1	0	1
Ristocetin polymyxin B		1	1		

The figures indicates number of Cases

(*one S albus and one B anitratum*) were resistant to ristocetin (total number tes is 34)

e VIII shows the effect of the above mentioned drugs on the elimination of ..eria in the respective treatment groups Gentamicin was able to eradicate all in nine out of 10 cases bacitracin neomycin and restocetin polymyxin B in ne instance each The other drugs were not able in any case When these were compared using the Fisher s exact test the effect of gentamicin was *significantly* ($P < 0\ 002$) *superior to the others after pooling their results*

Discussion

iluation of the present results the presence of S albus was definitely ered beside other potential pathogens since it has been demonstrated that nicroorganism may be the cause of postoperative intraocular infection ton et al 1973 Allen & mangiaracine 1974 Forster 1974 1976 Fahmy

clinical effectiveness of the examined drugs against infective eye diseases is tablished (Leopold & Apt 1960 Norn 1975 Havener 1978) However their on the normal bacterial flora seem to differ According to the present study entamicin was able to suppress the flora totally in almost all of the examined while the other drugs were ineffective although most of the strains were ve to the respective antibiotics and sulphonamide This may be due to the treatment period Locatcher Khorazo & Gutierrez (1956) found that S i was usually eliminated in 2 3 days while gram negative bacilli persisted as s 7 days no information was given as to the time needed to eradicate S albus : superiority of gentamicin in the treatment of ocular infections (Halasa 1967 uson & Suie 1967 Gordon 1970) reduction of postoperative flora (Burns et 58 1972) and pre-operative bacterial counts of the lids (Whitney et al 1972) en demonstrated However this powerful antibiotic does not seem to be the lrug for routine prophylaxis Its uncritical use will create the resistant strain ıay kill tomorrow s patient (Havener 1978) Nonetheless in certain instances is surgery on the last eye contaminated penetrating trauma or extensive tive procedures its application seems to be justified

: fact that most of the examined antibiotics have proved to be ineffective in the :limination of bacteria within the mentioned period of 18 h and the limited itions of gentamicin *may stimulate further studies to determine the effects of* antibiotics and eventually other alternatives when used in a longer period of ·e 8-10 days Such studies if performed on a larger series of patients may if fallen negatively – i e if bacteria were not totally eradicated – whether

potential pathogens do flourish and whether resistent strains ... claimed by Leopold (1958 1960 1971 1972)

Finally it has to be proved in controlled studies with bacterial ... cultures the actual value of total eye sterility at the time of surgery ... frequency of postoperative infection Such studies do not exist ... required

References

Allen H F & Mangiaracine A B (1964) Bacterial endophthalmitis after cataract ... A study of 22 infections in 20 000 operations *Arch. Ophthal. (Chicago)* ...

Allen H F & Mangiaracine A B (1964) Bacterial endophthalmitis after cataract ... II incidence in 36 000 consecutive operations with special reference to ... topical antibiotics *Arch Ophthal. (Chicago) 91* 3–7

Burns R P Hansen T Frauenfelder F T Klass A M & Allen A ... model for evaluation of human conjunctivitis and topical therapy ... 132–137

Burns R P & Oden M (1972) Antibiotic prophylaxis in cataract surgery ... *Ophthal. Soc 70* 43–57

Callahan A (1953) Effect of sulfonamides and antibiotics on panophthalmitis ... cataract *Arch. Ophthal. (Chicago) 49* 212–219

Dunnington J H & Locatcher Khorazo D (1945) Value of cultures before ... cataract *Arch Ophthal (Chicago) 34* 215–219

Fahmy J A Møller S Weis Bentzon M (1975a) Bacterial flora in relation to ... extraction I Material methods and pre-operative flora *Acta ophthal. (Kbh)* ...

Fahmy J A Møller S Weis Bentzon M (1975b) Bacterial flora in relation to ... extraction II Peroperative flora *Acta ophthal (kbh) 53* 4 6–491

Fahmy J A (1975) Endophthalmitis following cataract extraction ... 522–536

Forster R K (1974) Endophthalmitis diagnostic cultures and visual results ... *(Chicago) 92* 387–392

Forster R K Zachary I G Cottingham A J Norton E W D (19..) ... on the diagnosis cause and treatment of endophthalmitis *Amer J Ophthal* ...

Goodner E K (1963) Routine pre-operative and postsurgical management ... *3* 119–132

Gordon D M (1970) Gentamicin sulfate in external eye infections *Amer J* ... 300–309

Halasa A H (1967) Gentamicin in the treatment of bacterial conjunctivitis *Amer J* ... *63* 1699–1702

Havener W H (1978) Ocular pharmacology pp 114–185 Mosby St Louis

Leopold I H (1958) Comment to picos paper The management of ... following cataract extraction *Surv Ophthal 3* 358–360

Leopold I H Apt L (1960) Postoperative intraocular infections *Amer J* ... 1225–1247

Leopold I H (1971) Discussion in Chalkley & Schoch's (1971) paper ... antibiotics in cataract surgery *Trans Amer Ophthal Soc 69* ...

I I H (1972) Discussion in Burns & Oden s (1972) paper Antibiotic prophylaxis in ict surgery *Trans Amer Ophthal Soc 70* 43–57

her Khorazo D (1953) The effect on the ocular bacterial flora of local treatment with omycetin terramycin or penicillin streptomycin ophthalmic ointments in pre-opera ataract cases and miscellaneous infections *Amer J Ophthal 36* 475–479

er Khorazo D & Gutierrez E (1956) Eye infections following cataract extraction. *J Ophthal 41* 981 987

er Khorazo D & Gutierrez E (1972) Postoperative infection of the eye In Locatcher az & Seegal (Eds) Microbiology of the eye pp 77–85 Mosby St. Louis.

son R. H & Suie T (1967) Gentamicin sulfate in external eye infections *J Amer Med 99* 42,–428

I S (19,5) Antibiotic eye drops. Combination preparations with resiccetin *Ugeskr 13,* 2458–2460

on M J Brubaker R. F & Allen H F (1973) Staphylococcus epidermidas (albus) phthalmitis report of 2 cases after cataract extractions *Arch Ophthal (Chicago) 89* 6

v C. R. Anderson R. F Allensmith M R. (19,?) Pre-operative administered iotics Their effect on bacterial counts of the eyelids *Arch Ophthal (Chicago) 8* -160

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A HUMAN AND IN VITRO STUDY ON THE EXCHANGE Of [illegible] AND SOLUTES FROM SOFT CONTACT LENSES

BY

T SORENSEN F TAAGEHOJ JENSEN and J MARQ [illegible]

Elimination of technetium (pertechnetate in normal saline [illegible] studied from various types of contact lenses placed on normal human [illegible] means of computer assisted gamma camera using region of interest [illegible] with the designated area corresponding to the conjunctival sac

An elimination 4 times slower was found from a highly hyd[illegible] (Scanlens) than from a HEMA lens (Soflens) 0 [illegible] min and [illegible] tively From an ultrathin lens (U3 Soflens) was eliminated [illegible] lenses did not absorb the isotope

In a laboratory study the lenses were pre soaked in pertechnetate [illegible] washed at 2 min intervals in 0 5 ml saline By this procedure [illegible] technetium was eliminated from Scanlens 16% min from Soflens and [illegible] min from a thin therapeutic lens (Plano-T) The ratio Soflens Scanlens [illegible] the human study 4 0 and in the laboratory study 4 9 Rad[illegible] rapidly eliminated from CAB lenses

A similar study was carried out with radioactive water More than [illegible] was eliminated in the first 10 min followed by a slower eliminat[illegible] min Then an increased elimination was seen for a few min This [illegible] elimination was in repeated studies constantly found after [illegible] found in the studies with technetium and labelled leucine

Key words technetium – radioactive water – leucine – elim[illegible] – human – in vitro

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ous study on normal human persons demonstrated that the radioistope um was eliminated from soft contact lenses with 2%/min (Sørensen & oj Jensen 1980) To the best of our knowledge this was the first report on ination of solutes from soft contact lenses placed in situ on a human eye e present paper these studies are extended to other types of contact lenses he exchange of radioactive water and leucine in the lenses

Material and Methods

ers were selected from normal myopic persons wearing contact lenses All were l to the lenses at the time of the determinations

equipment consisted of a computer assisted gamma camera The radioisotope in the in vivo studies were technetium as pertechnetate in normal saline solut on A olume of this solution was instillated on the center of the contact lens while the eyelids were held apart a few seconds after the instillation The persons blinked normally in the position under the gamma camera with the head slightly turned to the side opposite to being investigated to avoid accumulation of the radioisotope at the outer canthal area gion of interest was the conjunctival sac area Radioactivity was recorded at 10 second ls and activity time curves were generated by the computer and plotted in a arithmic system Scintigrams v ere taken at the beginning and the end of the ination The results were presented as fractional turnover rates i e slopes of the time curves For detailed descriptions see Sørensen & Taagehoj Jensen 1977 1979 In man studies with contact lenses corrections for background components were not ry

e in vitro studies the lenses were pre soaked n saline with technetium at room ature The lenses were then blotted and placed n 0 5 ml saline This procedure was d at 2 min intervals for 98 min The radioactivity was recorded in the washing ns and the activity plotted in a semilogarithmic system Straight lines were approxima the method of least squares In the studies with radioactive water a similar procedure d but the study was extended using various washing olumes The study with leucine ried out at pH of about the isoelectric point and the other studies at near neutral pH vitro studies were made at room temperature

concentration of TcO_4 in the washing solutions was counted in automatic sample r NaJ (Tc)

$^{3}H_2O$ and ^{14}C leucine was determined by liqu d scintillation us ng Insta Gel and ib model 3003 Liquid Scintillation Spectrometre

lenses with different water content were investigated A highly hydrophilic lens ns = Duragel) and a daily wear lens (Soflens = HEMA) Thin lenses (L 3 and plano-T MA lenses with center thicknesses of 0 07 mm and 0 18 mm) were also studied The ens (cellulose acetate buthyrate) which has a very low water content was included in the study



F r 1A

Distribution of technetium in a normal human eye fitted with a h d conta e time about 10-30 seconds after instillation Radioactivity is seen in he c e the lacrimal drainage system but not in the nose

Fig 1B

Scintigram from the same ha d lens fitted perso n as in Fig 1A later, ed after instillation No radioactivity is accumulated in the hard lens the lacrimal sac and naso lacrimal duct are fi led by tracer which also has ente

Results

In Figs 1A 1B 2A and 2B are demonstrated the distribution of the about 0-0 5 min and 14.5-15 0 min after instillation. No radioac the conjunctival sac area in Fig 1B which is from a hard lens end of the determination A similar distribution is found in a hard contact lens In a soft lens fitted eye on the contrar accumulated corresponding to the position of the lens (F previous report (Sorensen & Taagehoj Jensen 1980) it was detec radioactivity was accumulated in the lens when the lens technetium before insertion as well as when the radioact eye fitted with a non pre soaked lens

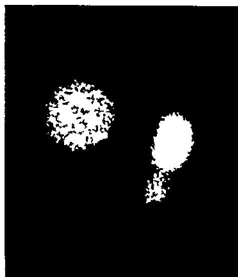


Fig 2A

ɔution of technetium in a normal human eye fitted with a *soft* contact lens Exposure ıbout 10-30 seconds after instillation The tracer has not entered the lacrimal duct. radioactivity is accumulated corresponding to the soft contact lens (in contrast to the hard lens in Fig 1A)

Fig 2B

ram from the *soft* lens fitted person from Fig ?A exposure time about 14 ɔ lɔ ıfter instillation Radioactivity is seen in the soft lens the lacrimal sac and in the nasolacrimal duct

ıe elimination curves from persons wearing hard contact lenses had a diphasic ınation as in normal eyes without contact lenses The elimination in the first 1 2 was very fast owing to rapid drainage of the surplus volume after instillation A

Table I

Elimination of technetium (TcO_4) from contact lenses Fractional turnover rate min ¹

		Initial phase	Basal phase
Hard lens	(n = 3)	0 272 (s = 0 009)	0 083 (s = 0 0?2)
Soflens	(n = 6)		0 020 (s = 0 004)
L3	(n = 4)	0 047 (s = 0 019)	0 0?4 (s = 0 003)
Scanlens	(n = 7)	0 010 (s = 0 00ɔ)	0 00ɔ (s = 0 007)

From Sørensen & Taagehøj Jensen (1980)

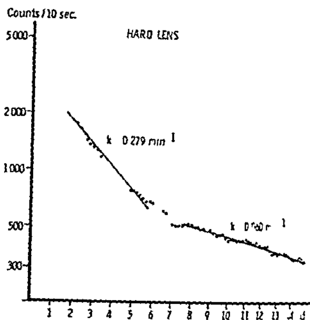
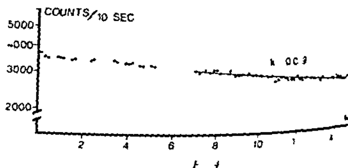


Fig 3

Activity time function curve from a hard lens fitted person. The curve has a ... without contact lenses a very rapid elimination of technetium ... an initial phase with a higher fractional turnover rate about ... from 7 15 min

higher initial phase was found about 2 ... min followed by a slower ... 7 15 min The results in Table I clearly demonstrate the difference ... and soft lenses In hard lens cases the elimination was in fact a ... because no radioactivity entered the lens



F 4

Elimination of technetium (TcO_4) from ... lens placed ...

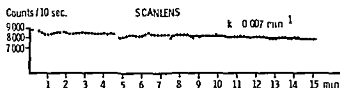


Fig 5

mination of technetium (TcO4) from a Scanlens® placed on a normal human eye

curves from persons wearing soft contact lenses (Fig 4) were quite different persons not wearing contact lenses The fractional turnover rates were much and diphasic elimination was hardly visible for Soflens (Fig 4) and Scanlens) whereas a difference between initial and basal phase could be seen on the from U3 lenses (Fig 6) The difference was at the 6% level (t test for paired

a previous study on ordinary Soflens lenses (Sørensen et al 1980) the onal turnover rate for the initial phase was not calculated because the curve d like a straight line over the entire 15 min The value for Soflens in Table I is he fractional turnover rate calculated in the time interval 7 15 min

e human eye with its microdimensions is impossible to copy in a laboratory 1 A very simple model might as well be as good as a refined one approximating hysiology of the human eye We used a very simple model which demonstrated ict differences between the lenses (Fig 7) The elimination of technetium from nses approximated fairly well to an exponential elimination From Scanlens eliminated about 3%/min and from Soflens 15 3% min Plano-T had the est elimination (about 28%/min) (Fig 7) The concentration of the radioisotope ie pre soaking saline solution was extremely low and estimated to about 3

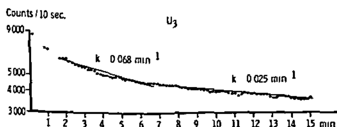


Fig 6

El mination of technetium (TcO) from an U3® lens placed on a normal human eye

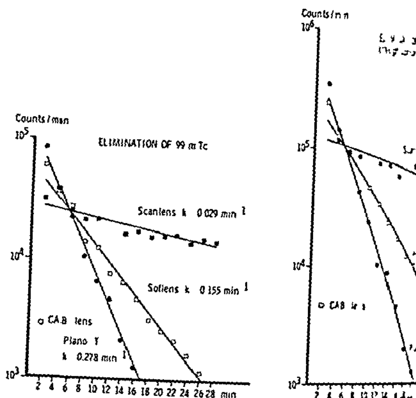


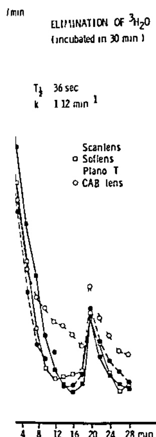
Fig
Elimination in vitro of technetium (TcO4) from various lenses

Fig 9
Elimination in vitro of technetium (TcO4 high concentration) from various

pmol l With high concentration of technetium with most of the Tc99 rated to Tc99 and a 1000 times higher concentration fractional turn the same magnitude was found (Fig 8) The ratio Soflens Scanlens studies 1 9 and in the human vivo studies 1 0 (Table I)

Only a small amount of technetium was absorbed by the CAB radioactivity was eliminated by the first washing procedure For the there seems to be no radioisotope other than technetium suitable studies Thechnetium is easily abvailable and can be safely used investigations

The elimination of solutes other than technetium have to be laboratory In this way the exchange of radioactive water was studied elimination of the radioactive water was found – a fraction of 11



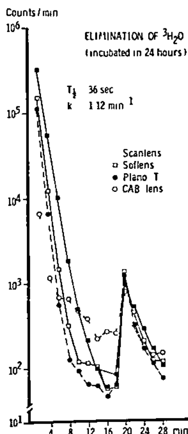


Fig 9

Elimination of radioactive water Incubation time of the lenses was 30 min

F g 10

Elimination of radioactu e water after an incubation time of 24 h

in in the time interval 0 10 min (Fig 9) From 10-20 min the elimination was : constant After 20 min the elimination suddenly increased to a level irable to the elimination in the 0-10 min interval This study was carried out ncubation of the lenses in the radioactive water for 30 min An incubation l of 24 h (Fig 10) resulted however in the same pattern of elimintion with a after 20 min The congruity of the curves is noteworthy even the CAB lens ed the hydrophilic lenses

hange of the washing volume from 0 5 ml to 5 0 ml did not influence the rkable exchange of water after 20 min in the lenses

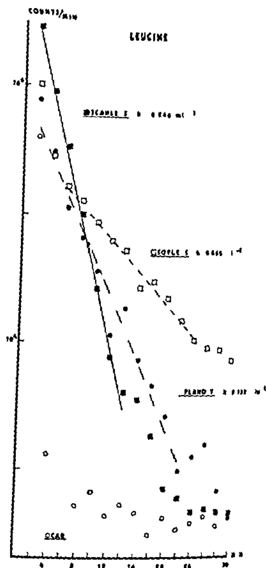


Fig 11
Elimination of leucine C_{14}

In the study with leucine Soflens turned out to have the slowest elimina (Fig 11) with a fractional turnover rate of 0 065 min [1] compared to Scanle min [1]) and Plano T (0 132 min [1]) In the studies with pertechnetate and ra water Scanlens had the lowest fractional turnover rate No peak with a elimination was found in the leucine study

Discussion

i it is a common assumption that soft contact lenses may act as a sustained
system for drugs and solutes introduced into the conjunctival sac, only a few
have been concerned with this topic There have been several studies on
rt of oxygen in soft contact lens materials (Fatt 1978) The elimination of
ine from soft contact lenses has been studied in vitro and in vivo in animals
ients with glaucoma (Hillman et al 1975 van Hoose & Leaders 1974
i 1971 Hillman 1974 Asseff et al. 1973 Krohn & Breitfeller 1975) These
showed that the biological response to pilocarpine was enhanced by the soft
lens The in vitro studies revealed an initially rapid release of the drug
d by a slower release This is fully in agreement with the theoretical
ion of a first order pattern of elimination (Richardson 1975) Using
tein as tracer a similar initial rapid release from the lenses was found
an & Kaufman 1970)

ie present study the negatively charged pertechnetate was used in the
inations on human subjects It is noteworthy that the slowest elimination was
ie most hydrophilic lens namely Scanlens The concentration was extremely
he soaking solutions and in the lenses. A higher concentration of pertechnetate
roportionally more disintegrated molecules) in the soaking solution in the in
udy resulted in the same fractional turnover rate (Fig 7 and Fig 8) In a
is paper (Sorensen & Taagehoj Jensen 1980) the same fractional turnover
is found when lenses were pre soaked in saline with the radioisotope and
he isotope was instillated on a non labelled lens on the eye The radioisotope
ntly rapidly penetrated the lens and was very slowly released from the lens
ifference between Soflens and Scanlens is probably dependant on the
nce in hydrogel material On the other hand the difference between Soflens
3 in the human study must depend on the difference in the amount of lens
al The U3 lens takes up relatively less radioactivity thus making the tear flow
from the conjunctival sac with its characteristic diphasic shape visible In the
ens persons this tear flow curve was seen because the hard lens did not take
radioisotope and the curve represented the elimination of technetium from
junctival sac The fractional turnover rate in persons with hard lenses cannot
verted to tear flow as in persons without contact lenses because the volume in
njunctival sac is not the same in the two situations. The same fractional
er rate will in a hard lens case correspond to a higher tear flow owing to the
oly higher tear volume in the conjunctival sac

difference between the elimination of technetium from Soflens and Plano-T
in vitro study can be explained by the difference in lens thickness of these
made of the same material The radioisotope was eliminated more rapidly

from the thinner lens The CAB lens probably did not take up pertechnetate small amount of radioactivity in the first washing solution could be the es surface adhesion

The simple laboratory model turned out to be in fair accordance with the b study since the ratio Soflens/Scanlens was 4 9 and 4 0 respectively in the studies

The exchange of water in the lenses was found to be more than 100% ma in vitro study In the in vitro study pertechnetate was eliminated 6-8 times than in the human study Corresponding to this the water should be exch with 14 19%/min if the lenses were placed in the human eye taking no acc the difference in temperature with the subsequent decrease in pore diameter lens material and decrease in viscosity of saline at higher temperature.

There is no obvious explanation for the elimination peak in the radioact study after 20 min Though the liquid structure of water is still debated one speculate that the dipol nature of water or hydrogen bonds could be respons the phenomenon It seems however more reasonable that a chemical bind water would manifest itself on the entire elimination curve and not as a single If a mechanical factor was responsible one would expect the peak to be plac different time interval using another molocule The study with leucine did no a peak like water in the 30 min determination time A somewhat similar pe found by Hillman et al (1975) in an elimination study of pilocarpine Af interruption of flow of eluting saline for a 15 hour overnight period, he elim of pilocarpine from the soft contact lens had a second peak

In contrast to the high water flow found in this study Fatt (1978) has that the amount of water driven through the lens was entirely negligibl reason for these diverging results is not obvious A relatively high diffusio water was found by Gumpelmayer & Schwach (1972 1973) The di coefficient for water in the hydrophilic materials were found to be smaller than the diffusion coefficient for water molecules in water They als a great variation of the diffusion properties in the various polymers – a pheno which was confirmed by the present study We found the slowest elimin pertechnetate from the most hydrophilic material This pattern was change leucine elimination study A similar change was found by Gumpelmayer & S (1972 1973) between glucose and amino acids

The diffusion of a solute through a soft contact lens is not solely depen the molecular size One has to consider the amount of hydration shell aro molecule the chemical binding to the lens material and the composition polymer At the present time it seems almost impossible to predict the diffus solute without testing

References

C F Weisman R. L. Podos S & Becker B (19"3) Ocular penetration of pilocarpine in tates Amer J Ophthal. 75 212–21ɔ

(19 8) Water flow conductivity and pore diameter in extended wear gel lens materials . J Optom. 5ɔ 43–47

(19/8) Physiology of the eye 1st edn Butterworths Boston London

elmayer T F & Schwach G W (19"9) Diffusion propert es of hydrophilic contact lens rials – A preliminary report Co tacto 16 11 17

elmayer T F & Schwach G W (1973) Diffusion properties of hydrophilic materials r J Opt m. 50 904–913

in J (19/4) Management of acute glaucoma with pilocarpine soaked hydrophilic lens J Ophthal. 58 674–6 9

in J (19/ɔ) Pilocarpine delivery by hydrophilic lens in the management of acute icoma. Trans Ophthal. Soc U K 95 79–84

loose M C. & Leaders F E. (19"4) The role of the cornea in b ologic response to carpine In e t Ophthal. 13 377–383

1 D L. & Breutfeller J M (197ɔ) Quantitation of pilocarpine flux enhancement across ated rabbit cornea by hydrogel polymer lenses In est Ophthal. 14 1ɔ2 1ɔɔ

an S & Reminger B (1971) Simulated sustained release pilocarpine therapy and eous humor dynamics. Canad. J Ophthal. 6 14 23

rdson K. (19/5) Ocular microtherapy Arch Ophthal (Chicago) 93 74 86

isen T & Taageboj Jensen F (19"") Methodological aspects of tear flow determination neans of a radioactive tracer Acta ophthal (Kbh.) ɔ5 "96 "38

isen T & Taageboj Jensen F (19/9) Tear flow in normal human eyes. Determination by ans of radioisotope and gamma camera. Acta ophthal (Kbh) ɔ" ɔ64–ɔ81

isen T & Taageboj Jensen F & Christensen L (1980) Tear flow and soft contact lenses. a phthal. (Kbh.) 58 182 187

nan S R. & Kaufman H E (19"0) Use for hydrophilic contact lenses to increase ocular etration of topical drugs Inv est Ophthal 9 2ɔ0–2ɔɔ

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CLINICAL TEAR ANALYSIS USING LASER DIFFRACTION

BY

DAVID MILLER WILLIAM J PLAUS and ROGER P ZELT

A diagnostic method has been developed to analyze tear specimens from patients with red eyes using the technique of laser diffraction. After proper tear sample preparation presence of a diffraction halo produced by the tear specimen indicates presence of an external ocular inflammation and helps rule out such conditions as glaucoma iritis and episcleritis Measurement of the size of the halo pattern may also be used to give information as to the concentration of cells in the tear sample

Key words laser diffraction – tears – tear cells – external eye disease halos

Patients with white blood cells in their tears will report seeing a slowly disap halo if asked to look at a light source in a darkened room The halo is be immediately after a blink and slowly fades until the next blink Such halos ar vivid in acute purulent conjunctivitis and obstruction of the nasal lacrimal duc

This phenomenon of a fading halo seen by patients with diseased eyes w noted by Descartes in 1637 (Simpson 1953) Later Simpson assuming th represented a diffraction pheonomenon measured the radius of the fad seen by his own eyes and calculated the size of cell in the tear film which prod to be about 8 μ Simpson further suggested that since the phenomenon w described by Descartes that it should be known as Descartes corona

Although a predicted value of 8 μ is a bit small for most inflammatory ce phenomenon might have clinical usefulness in screening for external eye dis a busy clinical setting

However the determination of the very presence of a halo as well as a

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is a demanding task for both patient and doctor in such a setting Thus a and more objective modification of the phenomenon is needed The ure suggests (Koch 1968 Wyatt 1968 Cram et al 1973 Jamieson et al 197ɔ) number of cell containing biological fluids will produce diffraction patterns in Therefore we have undertaken to study the tear samples from patients with ıal eye diseases using a laser diffraction technique The study further ıned the relationship of these diffraction patterns to those produced by pure ıspensions

Method

ar collection Specimens from the lower tear meniscus were collected with fine 10 µl capillary tubes polypropylene disposable tips attached to a 10 µl automatic micro e or directly onto the edge of glass slides Diffraction patterns of tear samples collected ach method were evaluated for pattern sharpness

ar preparation Once the tear sample was on the slide it was noted that mucous ınized cellular debris protein aggregates or lipoid globules could all obscure the cell ed diffraction pattern Thus similar amounts of isotonic solutions of the proteolytic papain (contact lens enzyme cleaner) the mucolytic agent N acetyl cysteine and the olytic agent salicylic acid as well as a combination of the three were added to separate amples from the same patient Diffraction patterns were then evaluated and compared Gram or Wright stained specimens under the light microscope In each case an attempt

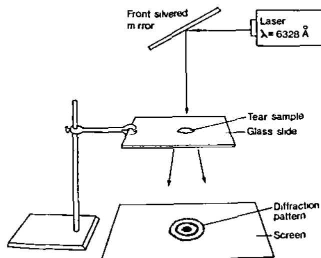


Fig 1
Apparatus used for laser diffraction of tear sample

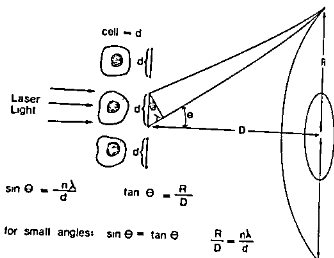


Fig 4
Diagram illustrating the path of light waves responsible for the diffraction pattern p by the cells in the tear sample

were done for each sample Cell diameter (d) in the sample was calculated using equa $\sin \varnothing = \frac{n\lambda}{d}$ were n = order of the maximum measured (1 in the example above) λ d = cell diameter and $\sin \varnothing = R/D$ (Fig 4)

F Clinical trials Once the system was made reproducible in the laboratory tear s were analyzed from 19 different patients with the following spectrum of external e d purulent conjunctivitis allergic conjunctivitis vernal conjunctivitis giant papillary co tivitis contact lens induced conjunctival irritation keratitis ectropion postoperative co tival irritation and pterygium

Results

A Tear Collection Tear samples collected with the 10 µl plastic disposable attached to the 10 µl micropipette consistently produced the sharpest and brig diffraction patterns

B Tear Preparation Papaine was the most effective of all the additives in reduc the amount of background amorphous material seen on stain and in sharpen the diffraction patterns

The diffraction patterns produced by the wet samples of the standard erythro tes neutrophils and lymphocytes more closely agreed with the accepted values

e than the dry samples (Bloom & Fawcett 1975) The dry samples yielded a m decrease in calculated cell size

example the mean of 9 samples of dry preparations of the same suspension blood cells produced a calculated cell size that was 11% smaller than from the samples when wet

ally isotonic preparations of the additives to the tear samples yielded ction determined cell diameters which correlated better with known cell size lid conventional pharmacologic concentrations of the additives

fluence of Cell Concentration Table 1 shows the relationship between ophil concentration (reflected in cells/mm²) and diameter of the first maxima fraction pattern The samples with an asterisk are from tears those without neutrophil suspensions isolated from blood Fig 3 is a graphic representation ble 1

nfluence of Cell Type Using the laser diffraction technique 9 samplings of a blood cell specimen yielded a mean first maxima diameter (2R) for a red cell nsion of 5 3 mm ± 0 15 mm for a lymphocyte suspension of 4 95 mm ± 0 10 and for a neutrophil suspension of 3 49 mm ± 0 10 mm

he laser diffraction pattern (Fig 2) is composed of a central bright red light ral maximum) surrounded by ever widening red circles (different orders of ma) separated by dark circles (different orders of minimum)

linical Findings The dilution studies in combination with the haematocytome howed that a tear sample must have at least 12 cells/mm² or about 1 or 2 cells high power field in order to produce an easily measurable laser diffraction rn Clinically speaking conjunctival inflammations of trace to 1+ reaction will

Table I
Cell concentration vs Halo size

Neutrophils/mm²	(2R) Diameter of First Maxima (mm)
400	8 2
86	3 8
54	3 5
44	3 3
18	3 3
12	3 1

* Neutrophils in clinical tear sample

Table II
Clinical Diagnosis vs Average Size Cell in Tears

	Clinical Diagnosis	Calculate Average Tear Cell Size ± SD	Microscopic Appearance of Tears
1	Allergic Conjunctivitis	7 3 μ ± 0 5	2+ Lymphocytes occasional squamous cells
2	Vernal Conjunctivitis	8 1 μ ± 0 5	4+ Lymphocytes rare squamous cells
3	Chronic Purulent Conjunctivitis	9 2 μ ± 0 5	3+ neutrophils 1+ lymphocytes 1+ squamous cells
4	Acute non traumatic purulent conjunctivitis	11 2 μ ± 0 5	3+ neutrophils 1+ lymphocytes
5	Acute purulent Conjunctivitis (1 day after ectropion repair)	11 6 μ ± 0 5	2+ neutrophil 1+ lymphocytes
6	Contact Lens Irritation	12 2 μ ± 0 5	3+ squamous cells

usually not produce enough inflammatory cells in the tears to give a meaningful pattern Thus conjunctival reactions of 2+ to 4+ would yield the best patterns

Is there any way of determining the predominant cell type in a tear specimen using this technique Krakau (1966) working with red blood cell samples showed that if cell concentration is known cell size can be approximated by the proper conversion factor Thus if we make the assumptions a) of a very high cell concentration (200 400 cells/mm²) and b) that the cells may arrange themselves in a uniform mesh we may take the calculated cell size (d) of equation (1) and then multiply (d) by 2 The resulting value suggests the diameter of the major cell present in the sample

Table II relates the calculated cell size using laser diffraction with the ... stained appearance of the tear specimen of high concentration as seen under the microscope for some representative cases

Discussion

The results of this study support the basic premise of Simpson that cells in the tear film caused by external ocular inflammation are responsible for the presence of

rtes halos The study further demonstrated that these halos could be duced in vitro in a rapid (1 2 min) procedure Thus one might forsee the when a patient with a red eye appears in a busy hospital emergency room a history is taken a nurse or trained technician takes a tear sample and rms a laser diffraction test The presence of a halo from the specimen may o rule out a diagnosis of iritis glaucoma or episcleritis for emergency room cian on duty

e question of the mechanism of the halos requires further discussion In a very ral way Fig 4 illustrates the events which produce the diffraction pattern The ion (Miller & Benedek 1973)

$$\sin \varnothing = \frac{n\lambda}{d} = \frac{R}{D} \quad (1)$$

e n = order of maxima

λ = 6328 mu (wavelenght of HeNe laser light

R = radius of first maxima

D = ditance of tear sample to screen

d = cell size

ribes the angular radius of a halo produced by a grating or mesh Thus one say that a meshwork of biological cells are related to a diffraction pattern in a ar way

owever the equation assumes a) theoretically optimal spacing between cells ell sizes of about twenty times the wavelength of light c) a significant rence in index of refraction between cell and surrounding media (ie tears and nt) d) uniform cell size e) uniform cell shape f) uniform orientation of g) even cell distribution Obviously our tear samples do not meet these ria Be that as it may can any further information be gained from the action pattern?

1966 Krakau working with blood samples of different concentration faced ame dilemma By assuming that the red cells behave like opaque discs he was to relate red cell size to the first maxima in very sparse cell preparations and concentration to the first maxima in dense preparations Our results with rent concentrations of neutrophils (Table I) also supports the concept that a relation between cells exists which changes with the spacing between the cells us with a high cell concentration it is the size of the cell clumps themselves ch determine the diffraction pattern However with low cell concentrations the cing between the cells becomes comparable to the size of the cell and the radius he first maxima is related to the cell size itself as in equation (1)

Therefore a few generalizations concerning cell concentration can be made from

the measurement of the diffraction pattern of a clinical tear sample and equals (1)

Concentrations of cells below 10 cells/mm² will probably be too sparse to p duce a pattern

Concentrations of between 10 o 100 cells/mm² allow enough spacing between cells so that inserting the radius of the first maxima of the halo will yield a cell size about 10 µ

Concentrations of cells above 100 cells/mm² produce a tighter network and insertion of the radius of the first maxima of the halo into equation (1) will give a calculated cell size of about 5 µ

In sum a tear sample yielding a laser diffraction pattern suggests an ext ocular inflammation with an inflammatory cell concentration of at least 10 cells/mm² If the radius of the halo is measured inserted into equation (1) and a value for d results in about 10 µ then the cell concentration is between 10 cells/mm² If the resultant d equals about 5 µ the inflammatory cell concentration is over 100 cells/mm²

References

Bloom W & Fawcett D W (1975) A Textbook of H stology 10th Ed W B Saunders Philadelphia

Cram L S & Brunsting A (1973) Fluorescence and l ght scattering measurements on cholera injected Pk 15 cells Exp Cell Res 78 209

Jamieson A M Schafer I A & Walton A G (1975) D fferential laser l ght scattering cultured human fibroblasts Biophys J 15 328A

Koch A L (1968) Theory of the angular dependence of l ght scat ered by bacteria similar sized biological objects J Theor Biol 18 133

Krakau C E T (1966) The diffraction pattern of dry blood smears B oph J 6 801

Miller D & Benedek C B (1973) Intraocular Light Scattering pp 83 86 C C Thomas

Simpson G C (1953) Ocular halos and coronas Brit J Ophthal 37 450

Wyatt P J (1968) Differential l ght scattering a phys cal method for den f ng bacterial cells Appl Opt 7 1879

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LACRIMAL PATHOLOGY EVALUATED BY DYNAMIC LACRIMAL SCINTIGRAPHY

BY

T SØRENSEN and F TAAGEHØJ JENSEN

This study of pathological lacrimal systems demonstrated the usefulness and sensitivity of dynamic lacrimal scintigraphy (dynamic use of computer assisted gamma camera) The method was very sensitive even small lacrimal obstructions caused a distinct change of the outflow curves This technique complements other tests in lacrimal assessment especially in patients eith epiphora and normal conventional tests

Key words lacrimal pathology – dynamic lacrimal scintigraphy – human – technetium – gamma camera

urate pre-operative assessment of the lacrimal drainage system is necessary and udes the demonstration of anatomical defects as well as the functional capacity he lacrimal drainage system This latter part of the assessment has in recent rs been possible by lacrimal scintigraphy In these studies on lacrimal scinti phy the evaluation has been carried out by comparing scintigrams at various rvals after instillation of the radiosotope or by measuring transit times to various ls of the lacrimal drainage system

n previous papers (Sørensen & Taagehøj Jensen 1977 1979) we have described technique of dynamic lacrimal scintigraphy" (i e outflow studies by dynamic of computer assisted gamma camera) and presented the results of these studies normal human subjects The amount of conjunctival transport in patients with ck in drainage systems and in normal persons was also reported

eived December 1 19 9

In the present study the dynamic lacrimal scintigraphy has been u ed patients with pathological changes of the lacrimal drainage s s em

Material and Methods

Pat ents attended to the Eye Department of Århus Kommunehosp al o e a period of two years compla ning of ep phora were included in the study Those who ured out a complete lacarimal obstruct on were excluded s nce these results ha e been presented previous paper (S rensen & Taagehoj Jensen 19 9)

The method was descr bed n deta ls n the papers men oned abo e It a ee emphas ze the importance of the head t lt oppos te to the eye be ng n es gated a correct method of nst llation with a man al fixat on of the e elds a few seconds instillation

All nvest gat ons were carr ed out w th the pa ent n the sup ne pos on preferred owing to the steady fixat on obtained n a plaster band ge during the recording t me W thout the hea l t lt in the sup ne pos on ea s accumulated at the canthal area (Sørensen & Taagehøj Jensen 19 9) but w th the head ti no accum seen and no d fference n tear flow between sup ne and upr ght pos on was dem

A volume of 10 µl of a normal sal ne solut on conta n ng echnetium as pertechnetate (100 00 µCi) as inst lled on the center of the cornea Sc n grams were taken and last 0 5 m n n the 15 m n record ng t m e By the region of in eres echnique ass gned area placed over the conjunct val sac area recordings were taken at intervals and curves were generated by the computer as act y me curves in a logarithm c plot These curves were used to e alua e the la rimal dra nage function Corrections for background components ere not carr ed out n th s s ud because he count rates were very h gh in most cases ow ng to the delayed ou flow n these patients

Results

The aim of this study was to demonstrate the nfluence of various pathological conditions in the lacrimal system on act vity time tear outflow curves (f dynamic lacrimal scintigraphy)

Def c ent tear secret on

Pat ent 1 a 33 year ld wo man had reduced tear secret on af er a skull fracture some months previous to th s in est gat on The pat ent ha l experienced a educed abil y to pr duce crying after the head trauma wh ch also re ul ed n b la eral s x h nerve pal but no a nerve palsy The Sch rmer tear test alues we e 4 and 9 mm 5 m n on righ and left respect vely Dynam c lacrimal sc nt graphy as normal n the ght e e Fig 1B d phas c el m nat on of the rad o sotope n a sem logarithmic plot as n normal eyes Fig (Sørensen & Taagehøj Jensen 1979) The fas e el m nation seen n normal eyes from the 5 m n after nst llat on (F g 2B) was a sumed to represent a h gher rat flow

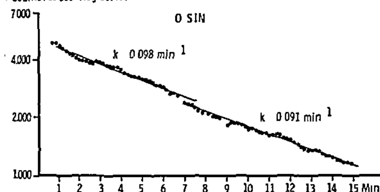
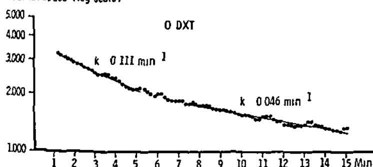


Fig 1A

w curve from patient 1 left eye Schirmer tear test was 2 mm ɔ min The surplus e is rapid eliminated from 0–1 min A diphasic elimination is not present in this eye th reduced tear secretion The slope of the curves k is the fractional turnover rate



F g 1B

ow curve from *patient 1 right eye A diphasic elimination is seen with a shift after* 5–7 min in this eye with the h gher Schirmer tear test (4 mm/5 min)

lation by the instillation procedure The patient s left eye (Fig 1A) was thus unable to nt a stimulated tear secretion whereas a slightly higher initial phase was found in the eye The patient had not experienced dry eye symptoms The very rapid elimination in ry *first min* caused by the rapid drainage of the surplus volume so tears after instillation 10 µl technetium solution

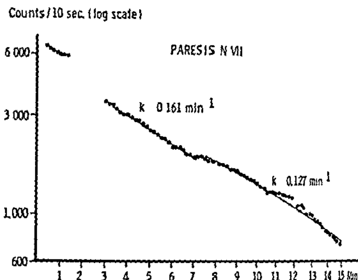


Fig 2A

Outflow curve from right eye patient 2 with epiphora owing to incomplete remnant facial palsy The rapid elimination of the surplus volume after instillation is missing diphasic elimination with a shift after 6–7 min is present but not distinct.

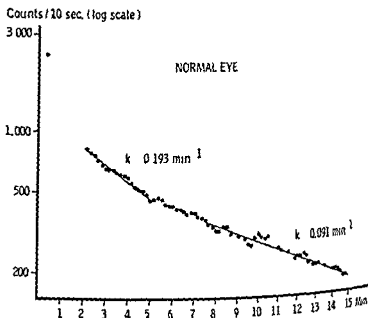


Fig 2B

Tear flow curve from patient 2's normal eye

l pump insufficiency

a 63 year-old man had a peripheral left facial nerve paresis of unknown origin with a ; of the left palpebral aperture but no lagophthalmus The Schirmer tear test was 20 ın The dynamic lacrimal scintigraphy was normal in the unaffected eye (Fig 2B) the paretic side showed a reduced ability to pass the purplus volume aftear on down the drainage system in the first 2 min (Fig 2A)

odic blinking

: *a 72 year-old man* referred to the hospital for dry eye syndrome The Schirmer tear 0 mm 5 min in both eyes Slit lamp examination was normal with a normal lacrimal nd no vital staining with Rose Bengal The patient suffered from spasmodic blinking w was completely normal (Fig 3) with a diphasic shape and a rapid elimination 0-2 er instillation This patient was apparently blinking the tears down the drainage hus avoiding absorption of the tears into the filter paper After 15 min tracer was ng the tear sac and nasolacrimal sac but no tracer entered the nose

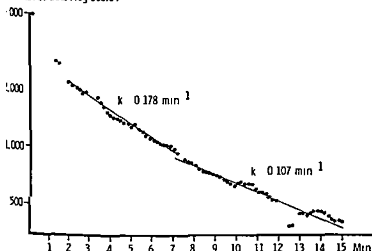


Fig 3
ow curve from patient 3 who suffered spasmodic blinking The curve is normal though the Schirmer tear test was 0 mm 5 min

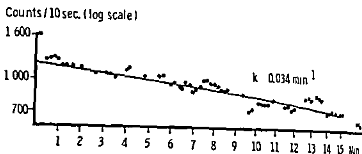


Fig 4
Tear outflow curve from patient 4 Pre sac stenosis owing to radiation for rodent ulcer in inner canthal area

Canalicular disease

Patient 4 a 50 year old man with atrophic skin and indurated subcutis at the medial can- area owing to radiation for rodent ulcer This patient had epiphora and dynamic lacrimal scintigraphy showed a reduced tear outflow with no initial phase (Fig 4). Small amounts of radioactivity were seen in the nasolacrimal duct after 15 min The lower canaliculus was completely occluded and the upper had a stenosis which was dilated with some success.

Calculus in the upper canaliculus

Patient 5 a 60 year-old woman with epiphora Tear flow was reduced and the tear flow curve was practically monophasic (Fig 5) Small amounts of radioactivity was seen in the [illegible] sac The drainage system was filled with mucus and a calculus was found in the upper canaliculus

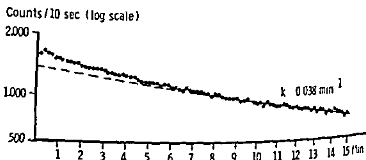


Fig 5
Tear outflow curve from patient 5 Calculus in the upper canaliculus and small amounts of mucus in the drainage system

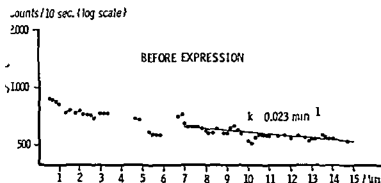


Fig 6A

…outflow curve from patient 6 who had a complete obstruction of the nasolacrimal duct. …urve was found when the drainage s stem was filled b mucus before expression of the lacrimal sac

…t 6 a 21 year-old man who had a fracture of the maxillary bone with subsequent …ion of the nasolacrimal duct and slight distension of the lacrimal sac Dynamic lacrimal …graphy was carried out before (Fig 6A) and after (Fig 6B) expression of mucus from …crimal sac The scintigram in Fig 6C was exposed 14–15 min after instillation of the …isotope The lacrimal sac was incompletely filled by the tracer After expression of the …s a new instillation of technetium resulted in a good filling of the lacrimal sac (Fig 6D)

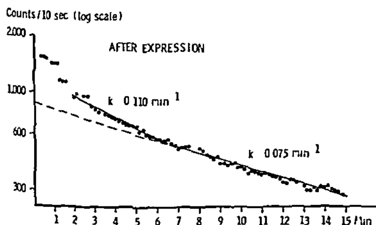


Fig 6B

…e from patient 6 after expression on the lacrimal sac A more rapid elimination is seen with a diphasic shape as in normal persons.

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THE OCULAR RESPONSES OF ORAL ADMINISTRATION PENBUTOLOL IN THE GLAUCOMATOUS PATIENT

BY

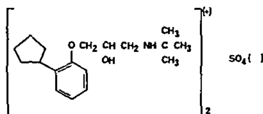
G K KRIEGLSTEIN E GRAMER and W LEYDHECKER

A single oral dose of 20 mg or 40 mg Penbutolol was given to two groups of untreated glaucoma patients The drug significantly decreased intraocul pressure and was dose related The IOP response was paralleled with decrease in pulse rate without significant effect on blood pressure In another group 27 glaucoma patients which were under sufficient IOP control following topical treatment with different antiglaucomatous agents the daily peroral treatment with 40 mg Penbutolol did not result in a further decrease of IOP However a significant drop in pulse rate could be noted over the four week period of treatment in this series of patients Blood pressure was similar to the single dose study not significantly affected Penbutolol treatment did not significantly change pupillary diameter quantitative tear flow or corneal sensitivity The potential usefulness of the drug in glaucomas with systemic hypertension or as additive treatment when topical treatment is insufficient is outlined

Key words glaucoma open angle – β blockers Penbutolol – oral therapy intraocular pressure

Penbutolol is a new promising β blocking agent which in the treatment of systemic hypertension has been found to be superior to Propranolol both in β-blocking potency and duration of action (Boksay 1979) Chemically this drug is a l-isomer of a phenoxyalkylamine derivative (( ) 1 tert butylamino 3 (2-cyclopentylphenoxy) 2 Propanol sulfate Fig 1) Pharmacologically Penbutolol can be characterized as follows The β blocking potency proved to be 4 5 times that of Propranolol experimentally and clinically It has only little intrinsic sympathomimetic activity about 50% that Alprenolol The drug produces little membrane stabilizing activity and has no cardio selectivity

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Penbutolol

Fig 1
The molecular structure of Penbutolol sulphate

ce betablockers are nowadays widely used in international medicine and
lly as antiglaucomatous drugs in ophthalmology there is a frequent therapeu
oss link between both fields Systemic betablocker therapy can affect the
omatous eye in different ways It may unfavorably influence arterial perfusion
are at the level of the optic nerve head It may represent a combined
peutic approach in ocular and systemic hypertension It may mediate chronic
al subsensitivity and/or produce dry eye syndromes The elucidation of part
se *questions* was the aim of the present study

Methods

resent investigation was subdivided into two series of clinical studies The first
as devoted to the acute effects of peroral administration of Penbutolol the
d one to the chronic effects of the same drug

al stud es Series I

series comprised two groups of open angle glaucoma patients (ten patients
The diagnosis of chronic open angle glaucoma was based on an untreated
level of more than 25 mmHg and or glaucomatous disc changes and or
omatous visual field loss Two of the above parameters were defined as
ssary for diagnosis None of the patients had received betablocker therapy in
ecent two months Miotic and adrenergic antiglaucomatous treatment was
ntinued *prior to the test for at least 48 h In all patients no other anterior*
ent pathology other than glaucoma was present there was no history of
laucomatous surgery in these patients Goldmann applanation tonometry

(same instrument same observer throughout the study) was performed be 4 h 6 h 8 h and 24 h after oral administration of 20 mg (first group of ten p or 40 mg (second group of ten patients) Penbutolol Blood pressure (sphygmo meter according to Riva Rocci) and pulse rate (using a stop watch) had measured in the same intervals Pupillary size (at the Goldmann perimeter standard light conditions) and quantitative tear flow (using Schirmers test recorded prior and 2 h as well as 4 h after drug application

Clinical studies Series II

Fifty three of 27 glaucoma patients had been investigated in this series The c for the diagnosis of chronic open angle glaucoma had been the same as in However the IOP of the patients of series II were controlled (≤ 99 mmH by topical antiglaucomatous treatment or by a successful antiglaucomatous procedure Patients with local or systemic betablocker therapy over the pa months were carefully excluded The following parameters were recorded (before Penbutolol administration) on day 14 and day 98 of Penbutolol 4? per day Intraocular pressure blood pressure pulse rate tear flow and c sensitivity (using the nylon monofilament aesthesiometer of Luneau Co Bonnet Frohnhauser/Munchen) Corneal sensitivity results were expre pressures of g/mm² to induce blinking reflex Duplicate readings were mad measurements the arithmetic means considered for statistics

Paired *t* test was used to to decide on the statistical relevance of the results.

Results

Series I

The effect of a single oral dose of Penbutolol on the intraocular pressure groups of ten glaucoma patients is demonstrated in Fig 9 90 mg and Penbutolol decreased IOP significantly The untreated pressure levels w and 28 3 mmHg on the average in the two groups The mean IOP response mg Penbutolol p o was 8 05 mg (according to 29% relative pressure reduct 11 5 mmHg after 40 mg Penbutolol p o (equivalent to a relative IOP dec 40 7%) The maximum of the resonse occured after 4 h the effect significant after 8 h However after 24 h post treatment the IOP did no from the pre treatment levels The drug response of the two dosages app significantly different confirming a dose response relationship Blood pres not affected in a statistically significant manner with either 90 mg or 4

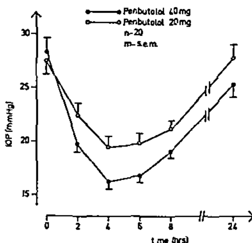
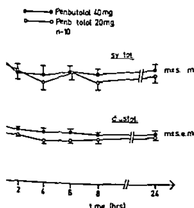


Fig 2

...ean time course of the IOP response of a single oral dose of 20 mg and 40 mg ...tolol in two groups of ten glaucoma patients. The abscissa gives the time after drug ...ation, the ordinate the IOP. Arithmetic means and standard errors of the means are presented



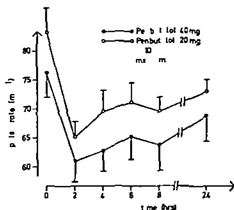


Fig 3

...ffect of a single oral dose of 20 mg and 40 mg Penbutolol in two groups of ten glaucoma ...ts on systolic and diastolic blood pressure. The abscissa gives the time course after drug ...ation, the ordinate the blood pressure. Arithmetic means and standard errors of the means are presented

Fig 4

...nean time course of a single oral dose of 20 mg and 40 mg Penbutolol on pulse rate in ...groups of ten glaucoma Patients (abscissa: time after drug application, ordinate: pulse rate). Arithmetic means and standard errors of the means are presented

Penbutolol There was a tendency towards a moderate systolic pressure dec which could not confirmed by statistics Blood pressure effects over the observation period are illustrated in Fig 3

With both Penbutolol doses a significant drop in pulse rate could be n after drug application which remained significant for 8 h After 24 h there some pulse rate reduction but this was not of statistical relevance (Fig 4)

Pupillary diameter exhibited no significant drug response with either Penbutolol (Fig 5)

This single dose study of series I did not verify an effect of Penbutolo flow as measured by the Schirmer test

Using 40 mg Penbutolol orally a slight decrease in tear flow was noted ou which could not be separated from reading error (Fig 6)

Series II

The mean IOP in the 53 treated glaucomatous eyes of this series before Pe administration was 19 3 mmHg Additive treatment with 40 mg Penbuto over 4 weeks resulted in a further decrease of IOP of 1 3 mmHg which statistically significant (Fig 7)

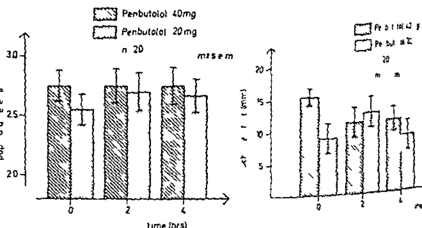


Fig 5
The effect of 20 mg and 40 mg Penbutolol perorally on pupillary diameter The ab the time after drug application the ordinate the pupillary diame er (arithmetic standard errors of the means)

Fig 6
The effect of 20 mg and 40 mg Penbutolol on quantitative tear flow The abscissa time after drug application the ordinate the wetting distance as indicated by Schi The columns indicate arithmetic means the vertical bars the standard errors of th

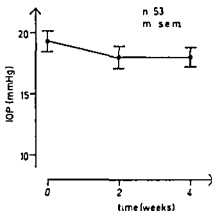


Fig 7

n IOP response of a 4 weeks treatment of 27 glaucoma patients (53 eyes) with 40 mg Penbutolol daily (arithmetic means and standard errors of the means)

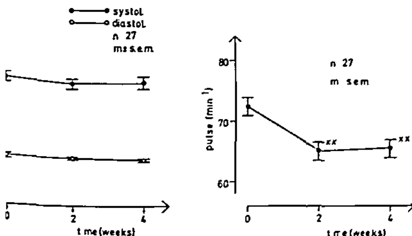


Fig 8

ect f additive Penbutolol treatment (40 mg per day) in 27 glaucoma patients on and diastolic blood pressure The abscissa gives the time f treatment the ordinate the blood pressure (arithmetic means ± standard errors)

Fig 9

ect f Penbutolol treatment over 4 weeks on pulse rate in 27 glaucoma patients time f treatment ordinate pulse arithmetic means ± standard errors) XX means statistically significant at the 0 01 level

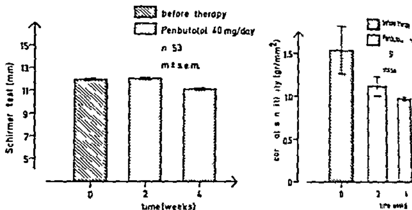


Fig 10

The effect of Penbutolol treatment on quantitative tearflow as measured by Schirme
(column with oblique lines before treatment columns with dotted pattern after tre
The abscissa gives the duration of treatment the ordinate the wetting distance in S
test.

Fig 11

The effect of Penbutolol peroral treatment on corneal sensitivity in 31 eyes of
patients Corneal sensitivity is expressed in pressure per square millimeter to trigger
reflex The column with oblique lines gives the parameter before treatment the
columns after treatment. The vertical bars indicate the standard errors of the mea

Systolic and diastolic blood pressure (mean baseline level 154 mmHg
mmHg diast) were not essentially changed over the 4 weeks period of Pen
treatment in these patients However a considerable effect highly significant
be identified in pulse rate The pre treatment pulse rate was 79 min-1 9 and 4
after treatment 65 min-1 (Fig 9) Schirmer test before, 2 and 4 weeks
Penbutolol treatment revealed no effect of the drug on tear flow The
distance on the filter paper was essentially unchanged and about 11 mm F
The evaluation of corneal sensitivity showed a tendency towards increase of se
during the treatment phase However because of the fairly high reading e
this semi-quantitative technique the differences were not significant (Fig 11).

Discussion

The result of the present study indicate that a single oral dose of Penbu
capable of reducing intraocular pressure in untreated glaucomas in a dose
significant way The magnitude of pressure reduction turned out to be com

most effective topical antiglaucomatous drugs commonly used in clinical

The time course of the IOP response was paralleled with a decrease in rate without a significant effect on blood pressure This cardiodepressive of the drug can be of crucial importance for the disease process when the matous damage of the optic nerve head is mixed with anterior ischemic pathy of the papilla In this respect Ohrstrom & Pandolfi (1978) reported an se of glaucomatous field loss with long term treatment of glaucoma with nic Propranolol in five out of 17 patients In an other paper the same author trom 1973) recommends use of a dose of the systemic β blocker which is erent for blood pressure Since we know that peripheral ischemic conditions lative contraindications for β blocker therapy (Dietz et al 1978) the dissocia f IOP response and blood pressure response by dose appears advisable In its with unsufficient IOP control by traditional antiglaucomatous topical nent systemic β-blocker therapy can add the necassary pressure reduction and glaucomatous nerve damage without the concern of lowering arterial sion pressure in the tissues which are at risk This combined effect of miotics eroral β-blocker was extensively established by Wettrel (1977) using Propra Practolol and Atenolol If we consider that the maintained long term IOP of β blocker is about half of the acute response the aspect of combined nent receives even more support (Drance 1970 Krieglstein 1978 1979) The ffect during the 4 weeks follow up under Penbutolol treatment was insignifi because the pressure in these patients was fully under control by other aucomatous therapy The decrease in pulse rate and the lack of significant nse on blood pressure was in agreement with the single dose study

ither in single dose nor in multiple dose investigations could we identify a icant effect on quantitative tear flow by the Schirmer s test There are mental data that β_1 receptors are involved in the regulation of tear flow g et al 1979) and there are clinical data confirming transitory manifestations eyes in the long term treatment with β blockers (Nielses & Eriksen 1979) that his parameter interest in β blocker glaucoma therapy A more careful follow er longer periods of time in elderly glaucoma patients who are borderline with tear flow capacity will shed further light on this problem

in all other β blocker studies in ophthalmology an influence of the drug on pupillary diameter could not be verified There is in fact β-adrenergic nation of the sphincter muscle of the pupil in the primate eye (Zimmermann & r 1979) which in the human is obviously not relevant compared to α nergic and cholinergic tonus of the iris

nbutolol has little membrane stabilizing activity Nevertheless a decrease in eal sensitivity due to chronic submaximal anaesthesia could not be confirmed he semi-quantitative technique applied In contrast a tendency towards an

increase in sensitivity was observed and it is speculative that subliminal a... may result clinically in over sensitization Using a prototype instrument fr... siometry in qunatitative manner Buhr & Draeger (1979) found a significa... sensitivity of the cornea in topical β blockers and even in those which... supposed to have no membrane stabilizing activity such as Timolol (Zimmer... Kaufman 1977)

Looking back to the initial questions raised in the introduction one may co... in the light of the present results that Penbutolol may represent a useful p... glaucoma therapy in patients who require systemic β blockers for interna... Penbutolol could possibly also be of value in patients who need additi... reduction on top of their local antiglaucomatous regimen Further clinical ... tion is warranted to establish the maintained effect of Penbutolol per... untreated glaucomas

References

Aberg G Adler C & Wikberg J (1979) Inhibition and facilitation of lacrimal ... β adrenergic drugs *Acta ophthal (Kbh)* 57 925–935

Boksay I (1979) Lecture at the 80th Annual Meeting of the American Society for C... Pharmacology and Therapeutics Kansas City

Buhr H & Draeger J (1979) Untersuchungen zur lokalanasthetischen Wirkung... Betablocker 77 Tagung der Deutschen Ophthal Gesellschaft in Heidelberg

Dietz A Wiese K H & Walter J (1978) Therapeutische Moglichkeiten und Grenzen ... Anwendung von Beta blockern *Klinikarzt* 7 943–959

Drance S M (1970) Use of sympathomimetic and sympatholytic agents of the glauc... Symposium on ocular pharmacology and therapeutics Trans New Orleans Acad O... Otolaryng Mosby/St Louis

Krieglstein G K (1978) Die Wirkung von Timolol Augentropfen auf den Augeninne... bei Glaucoma simplex *Klin Mbl Augenheilk* 172 677–685

Krieglstein G K (1979) Response of the Intraocular Pressure to Various β-blocki... In Krieglstein G K & Leydhecker W (Eds) Glaucoma update Springer Berlin... berg New York

Nielsen N V & Eriksen J S (1979) Timolol Transitory manifestations of dry ey... term treatment *Acta ophthal (Kbh)* 57 418–424

Wettrell K (1977) Beta adrenoceptor antagonism and intraocular pressure A clinic... on Propranolol Practolol and Atenolol *Acta ophthal (Kbh)* Suppl 134

Ohrstrom A (1973) Clinical experience with Propranolol in the treatment of glauc... *ophthal (Kbh)* 51 639–644

Öhrstrom A & Pandolfi M (1978) Long term treatment of glaucoma with... Propranolol *Amer J Ophthal* 86 340–344

Zimmerman T J & Kaufman H E (1977) Timolol A new β-adrenergic agent ... treatment of glaucoma *Arch Ophthal (Chicago)* 95 601–604

Zimmerman T J & Boger W P (1979) The beta adrenergic blocking a... treatment of glaucoma *Surv Ophthal* 23 347–369

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A MULTICENTRE STUDY OF THE EFFECT AND TOLERANCE OF OCUSERT P 40

BY

T ÅKERBLOM E AURELL[2] J CRISTIANSSON[3] V KRIISA KUNNOS[4] and O WIEBERT[5]

The su tabil ty of treatment w th Ocusert® P-40 a lamellar system inserted in the eye and allow ng the constant release of p locarp ne was stud ed n a group of pa ents (age range 43 83 years) with w de angle glaucoma Those patients completing a 3 week trial were included in an 8 month follow up study n wh ch the long term efficacy and tolerance of Ocusert® were stud ed

Treatment was d scontinued in 13 of the 42 pat ents n the 3-week trial ow ng to n t al irritation and retention problems (n 11) or unsatisfactory control of the intraocular pressure (I O P) (n 2) Of the 29 patients entering the long term study two were w thdrawn because of tolerance problems and two as a result of unsatisfactory control of I O P The 25 pat ents complet ng the study cons dered the Ocusert® system more conven ent and less l able to produce troublesome s de-effects than their prev ous therapy Ocusert® was best tolerated by the younger pat ents

Key words glaucoma intraocularpressure Ocusert® p locarp ne

rpine has been used to reduce the intraocular pressure in glaucoma patients bout 100 years The substance is generally administered in the forms of ops Optimal treatment with eyedrops usually entails frequent administration patients therefore have difficulty in complying with the treatment (Speath Vincent 1972) Pilocarpine drops also cause side effects above all in the form opia and miosis These reactions occur shortly after administration and are o temporary high concentrations of the drug in the eye Ocusert ® P-40 has

ed July 11th 19 9

been developed in attempt to overcome these problems It consists of a [illegible] elliptical lamella which is placed in the upper or lower fornix In co[illegible] tears pilocarpine is released at a constant rate over a 7-day period excep[illegible] first few hours when the rate of diffusion is higher

The Ocusert® system has been shown in clinical studies to produce a [illegible] reduction in intraocular pressure (I O P) over 7 days (Frauenfelder et al 1[illegible] Quigley et al 1975) The product also allows the same effect to be obtained [illegible] smaller amount of drug compared with administration in the form of [illegible] (Armaly & Rao 1973) Together with the continuous release this has [illegible] considerable reduction in the side effects produced by pilocarpine. The [illegible] of myopia and miosis has been consistently low (Place et al 19[illegible])

Certain patients experience initial difficulties in inserting and wear[illegible] lamellae (Henning 1976) although with thorough information and [illegible] training these problems can be reduced It is unlikely however that all [illegible] patients will tolerate the lamellae The aim of this investigation was to dete[illegible] which patients are best suited to using Ocusert® The patients who comp[illegible] first part of the study were subsequently kept under observation in order to [illegible] the long term effects of Ocusert®

Material and Methods

The Ocusert® system

The Ocusert® developed by the Alza coporation in the USA comprises three [illegible] layers (Fig 1) The middle membrane consists of pilocarpine bound to alginic ac[illegible] placed between two layers of ethyl vinyl acetate which determine the rate of d[illegible] drug from the system In contact with the tears pilocarpine is released at a constant ra[illegible] µg/h^{1} with the Ocusert® P 20 and 40 µg/h^{1} with the Ocusert® P-40 which was used [illegible] study) over a 7-day period During the first 1[illegible] h however the rate of diffusion [illegible] this is known as the burst effect

Patients

Only patients previously treated with miotics for open angle glaucoma [illegible] included in the study Some patients were also receiving adjuvant treatment [illegible] adrenaline or acetazolamide A condition of inclusion was that the patient's IO[illegible] was well controlled with conventional treatment

Forty two consecutive patients with a mean age of 63 years (range 4[illegible] years) were selected for the study At the start of the study 34 patients had [illegible] papilla and/or visual field defects Eight patients had an abnormal IOP [illegible] normal papilla and no detectable visual field defects These patients were [illegible] prophylactic treatment for ocular hypertension All patients had previous[illegible]

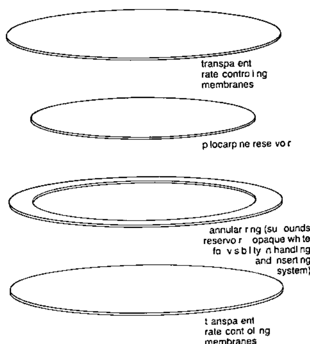


Fig 1
The Ocusert® system

d with miotics for at least one month (mean 28 months) Thirty eight patients using pilocarpine solutions of varying strength (1-4 %) and twelve were also ing adjuvant treatment with adrenaline or acetazolamide This treatment was ued unchanged during the study except in one patient who stopped using aline owing to an allergic reaction Two patients had previously been treated carbacholine and the remaining two had used physostigmine and demecari ide and adrenalin respectively

term study

patients were given detailed information about the aims and procedures of the before being included in the trial After general examin ation of the eye the l field was investigated by means of a Goldmann perimeter and the intraocular sure was determined using a Goldmann appl in ation tonometer Measurement e I O P was performed on average 2 h after the l ast instillation of miotic drops

Miotic treatment was then discontinued and the patient was given detailed and written instructions about the use of the lamellae The patient was given the opportunity to practice inserting and removing the lamella. The patients returned for examination after 3 9 and 21 days at which times the I O P and tolerance of Ocusert® was recorded

Long term study

The patients who completed the short term study were subsequently admitted to a follow up study the I O P and tolerance being recorded after 4 and 8 months of treatment The patient s visual field was investigated before the start of treatment and after 4 and 8 months

Results

Short term study

Substitution of Ocusert® for pilocarpine drops was achieved without any initial problems or changes in I O P in 29 of the 42 patients These 29 patients were subsequently included in the long term follow up of Ocusert® P-40 treatment

One patient discontinued the study as he was not capable of managing medication with either drops or Ocusert® Two patients were withdrawn from the study owing to unsatisfactory pressure control The remaining 10 patients who dropped out had so much difficulty tolerating the treatment that they preferred to revert to their previous treatment In most cases this happened during the first days of treatment The main problems were that the patients dropped the lamellae or found them irritating to their eyes

Long term study

Of the twenty nine in the long term follow up study one was an alcoholic and discontinued the treatment after one month Three patients reverted to their previous treatment (pilocarpine 2% pilocarpine 4% and physostigmine respectively) as their I O P s rose One of these patients also exhibited progressive visual field defects after three months

The remaining 25 patients completed 8 months treatment. Two patients were given adjuvant therapy with pilocarpine and adrenaline drops respectively as their I O P s tended to rise As the follow up period was largely a tolerance study these two patients were still included in it No significant change of the IOP was registered in the 25 patients during the 8 months of the study (Table I) nor was any change in the visual field detected in these patients

Table I

Mean I O P in the 25 patients who completed both parts of the study

eatment	Previous treatment	Ocusert® P-40 system				
nent time		4 days	7 days	3 weeks	4 months	8 months
mber of eyes	45	45	43	45	45	45
mmHg	20.9	21	21.3	20.8	21.9	21.4
	0.66	0.53	0.50	0.54	0.58	0.59

most common side effect of previous treatment was altered vision after tion of miotic drops Fourteen patients considered this troublesome (Table hese side effects declined markedly within one week of the start of Ocusert® ent.

ing the first few days of treatment with Ocusert® many patients dropped the a. This problem was probably partly due to the lamella being placed in the conjunctival sac Initially the patients were recommended to insert the rt® in the lower fornix but with time most patients found it easier to use the fornix The problem therefore decreased as the patients became accustomed treatment

Table II

Side effects reported by the 25 patients who completed both parts of the study

reatment		Previous treatment	Ocusert® P-40 system				
tment time			4 days	9 days	3 weeks	4 months	8 months
tion		2	3	2	3	4	6
ased secretion		3	5	2	4	3	3
ed vision		14	2	1	1	0	0
ella							
ped	0		12	14	14	11	16
	1 2		12	7	8	7	3
	3–4		1	3	1	3	3
	≧5		0	0	2	3	3

onjunctival injection

ne patient reported discharge of pus from the eye during one period

ne patient did not state the number of lamella dropped

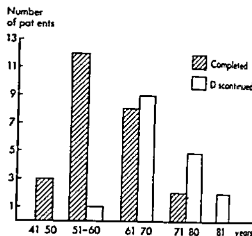


Fig 2
Age distribution of patients who completed discontinued the stud

All 25 patients who completed the study wished to continue on Ocuse treatment as they experienced little or no alteration in their vision, in com their previous treatment with miotic eyedrops They also found the Oc lamella more convenient and experienced a greater sense of freedom as t longer needed to have their bottle of pilocarpine drops constantly within rea

As shown i Fig 2 the younger patients had no difficulty in switching Ocusert® system The change of therapy caused increasing problems with inc age

Discussion

Treatment with pilocarpine eyedrops often causes side effects in the fo transient myopia and miosis However both patients and doctors have a these side effects up to now as being inevitably linked with pilocarpine trea The theoretical superiority of the Ocusert® lamella is therefore readily acc particularly by younger patients Compared to pilocarpine eyedrops, the O lamella requires somewhat greater manual dexterity Initially the patient s accept and endeavour to tolerate the feeling of having a foreign body in th The above factors may limit the number of glaucoma patients who are suited form of treatment

The results of the short term study also show that the patient should be advice and encouragement during the first few weeks of treatment in ord

ne any initial problems This requires a positive attitude on the part of the Many patients will otherwise be deprived of the benefits of the treatment.

Ocusert® lamella may with advantage be combined with other glaucoma both as drops and as tablets In this situation too the patient will iate minor improvements in the treatment schedule

change-over from previous treatment (most patients were previously treated locarpine solutions 2-4%) to Ocusert® generally caused little or no change in in those patients who could tolerate the Ocusert® system The pilocarpine tration in the lamella may therefore be considered sufficient for many s Although 13 patients dropped out of the initial 3 week study in only two as this due to inadequate control of I O P During the long term study a three patients reverted to treatment with drops for this reason and in two ipplementary treatment with drops was necessary

study has shown the Ocusert® lamella to be a valuable therapeutic alternative ing and middle aged glaucoma patients It is unlikely however to solve the ms involved in treating elderly glaucoma patients who need assistance from eople

Acknowledgement

hors wish to thank AB Hassle Molndal Sweden for the supply of Ocusert®

References

M & Rao K R (1973) The effect of pilocarpine Ocusert with different release rates ular pressure *Invest Ophthal* 7 491–496

Felder F Shell J Herbst S (1976) Effect of p locarpine ocular therapeutic systems on al control of intraocular pressure *Ann Ophthal 8 1031 1039*

g J (1976) Pilocarpintropfen – Ocusert – Pilocarpin Eine vergleichende Unter ing *Klin Mbl Augenheilk 169* 112–115

Fisher M Herbst S Gordon L Merrill R (1975) Comparative pharmacologic s of pilocarpine administered to normal subjects by eyedrops or by ocular therapeutic ns *Amer J Ophthal 80* 706–712

H Pollack I Harbin T (1975) Pilocarpine Ocuserts long term clinical trials and ed pharmaco-dynamics *Arch Ophthal (Chicago) 93* 771–775

G L (1970) Visual loss in a glaucoma clinic I Sociological considerations *Invest ial 9* 73–82

t P (1979) Patient s viewpoint of glaucoma therapy *Sighta Rev 42* 213–221

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TIMOLOL VERSUS PILOCARPINE SEPARATELY OR COMBINED WITH ACETAZOLAMIDE-EFFECT ON INTRAOCULAR PRESSURE

BY

B CALISSENDORFF[1] N MAREN[1] K WETTRELL[2] and A. ÖSTBERG

Fifty-eight patients with intraocular hypertension or primary open angle glaucoma participated in a double masked randomized study Timolol in concentrations 0 25% and 0 5% was compared with 1 % or 4% pilocarpine. Acetazolamide (250 mg × 3) was added if intraocular pressure (IOP) was uncontrolled with the highest concentrations tested.
No statistical difference was found in hypotensive effect between pilocarpine and timolol neither on ocular hypertensions nor glaucomas. The additive hypotensive effect of acetazolamide was the same for both substances. Once a day administration of timolol was sufficient in 17 of 90 cases controlled merely by topical administration

Key words timolol – pilocarpine – acetazolamide – once a day administration – additive effect – comparative study

Timolol maleat (Blocadren) a β-adrenoreceptor blocking substance was [illegible] introduced by Hall et al (1970) Topical treatment with timolol was found to [illegible] intraocular pressure (IOP) both in healthy volonteers (Katz et al. 19 [illegible]) and [illegible] with elevated IOP (Zimmerman & Kaufman 1977a,b) Several comparative [illegible] have shown that timolol administered twice a day has equally high hypotensive effect as pilocarpine (Bischoff 1978 Boger et al 1978 Katz 1978 Plane et al [illegible] Radius et al 1978 Airaksinen 1979 Diamond et al 1979 Schiffer 19[illegible] [illegible] according to Zimmerman & Kaufman (1977b) the effect of one single application of timolol persists more than 24 h The aim of this paper was to study to what extent

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potensive effect of timolol once a day was sufficient and comparable to pine administered four times a day

urther purpose of the study was to compare the additional effect of oral olamide in cases uncontrolled by topical therapy

Material

ight patients with primary open angle glaucoma or ocular hypertension were d for a double masked study (Table I) Forty patients were examined at the *sity Hospital Huddinge and 18 patients at the Central Hospital in Skovde* fference according to age IOP or other parameters were found in the two als which have therefore been pooled

criteria for admission to the study was an untreated IOP of > 22 mmHg by iann applanation tonometry The pressure is a mean value of two measure separated by at least one h The eye with the highest pressure determined the quent treatment for both eyes Forty-one patients already receiving therapy ucoma or ocular hypertension were instructed to discontinue their previous ation for one week Nine patients had their washout period shortened since e of IOP was suspected to be harmful In one case with a tendency to corneal ia and IOP of 38 mmHg the therapy was already started on the third day In s all with glaucomatous changes and IOP above 30 mmHg (mean 34 5) the y was started on the fourth day and in another 4 cases (3 glaucomas 1 ocular tension mean IOP 32) therapy started on the fifth day

criteria for glaucoma were defined as glaucomatous visual field defects ding to Goldmann perimetry and or glaucomatous cupping of the optic disc C/D ratio of at least 0 8 or documented progress of the cupping According s definition 34 patients in the study were considered to have open angle oma and the rest 24 were defined as ocular hypertension

e drugs used were timolol maleate in concentrations of 0 25% and 0 5% or rpine in concentrations of 1% 2% and 4% The substances were packed in

Table I

	Sex	Mean age (range)	Ocular hyper tension	Glaucoma
Pilocarpine	17 M 11 F	68 (54-80)	10	18
Timolol	14 M 16 F	67 (51 84)	14	16

identical bottles marked Vial A, B and C respectively. For the timolol gr... corresponded to 0.25% once a day, Vial B to 0.5% once a day and Vial C ... twice a day. For the pilocarpine group Vial A equalled 1%, Vial B ... 4% four times a day.

In a randomized fashion the patients entered the timolol or pilocarpine ... and continued in their respective groups throughout the study. One of ... investigators, uninformed of the actual therapy, interviewed and examined ... patient while the other determined the therapy and informed the patient.

Thirty patients were treated with timolol and 28 with pilocarpine. The treat... started with Vial A and after one week the IOP was measured. If uncontr... (< 22 mmHg) the treatment was changed to Vial B. After another week the IOP ... recorded, and if still uncontrolled Vial C was given. If IOP was not even ... on Vial C, concomitant oral therapy with acetazolamide 250 mg x ... When a patient reached an IOP of less than 22 mmHg receiving Vial A, B, C or ... combination with acetazolamide, he was maintained on this therapy and ex... after 2 and 6 weeks. Before and during treatment visual acuity, appl... tonometry, slit lamp observation and funduscopy were performed and ... visual fields, blood pressure and pulse were recorded.

The statistical analysis was based on the eyes with highest IOP and the ... signed rank test was used.

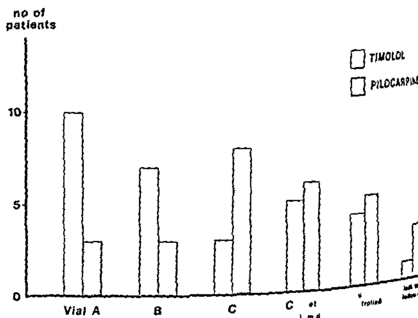


Fig 1
Distribution of patients according to final treatment.

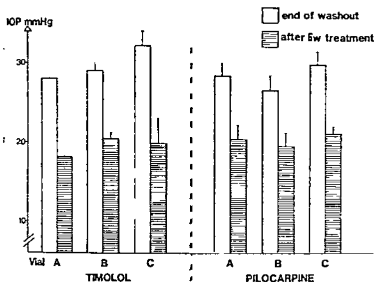


Fig 2

untreated IOP in mmHg ± SEM and mean IOP after 6 weeks therapy in 34 patients (20 timolol 14 pilocarpine) regulated by topical treatment

Results

listribution of patients according to final treatment is shown in Fig 1 Twenty patients were controlled with topical timolol of which 17 (9) with administra only once a day (the figures in brackets refer to the number of included angle glaucomas) Five (3) more patients were regulated with timolol and tolamide in combination Four (3) patients remained uncontrolled and 1 (0) nt was lost to follow up

the pilocarpine group 14 (10) patients were controlled with topical therapy her 6 (3) needed additional acetazolamide while 5 (4) remained uncontrolled } (1) were lost to follow up There exists no statistical difference between the per of patients controlled on topical timolol and pilocarpine respectively and potensive effect is the same in both glaucomas and ocular hypertensions

Fig 2 the untreated base line IOP and the IOP after 6 weeks maintenance py is shown No statistical difference is found in base line pressure between the arpine and the timolol group The mean pressure decrease for topical timolol or Vial A 9 9 mmHg Vial B 8 6 mmHg and Vial C 12 4 mmHg Correspond igures for pilocarpine were 7 0 7 0 and 8 8 mmHg Some patients (4 from the arpine group and 5 from the timolol group) showed a tendency to therapy

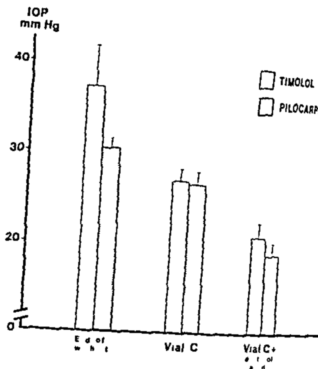


Fig 3

Mean untreated IOP in mmHg ± SEM mean IOP with maximum topical treatme and mean IOP with concomitant acetazolamide in 11 patients (5 timolol 6 p regulated by topical treatment and additional acetazolamide

escape They had an IOP < 21 mmHg at the end of the dose adjustment but after 6 weeks maintenance therapy the IOP was 24 0 and 23 4 in re group

The additional IOP lowering effect of acetazolamide in patients not contr Vial C was equal for the timolol and the pilocarpine group (Fig 3)

In 3 persons (2 in the timolol and 1 in the pilocarpine group) a su progress of glaucomatous visual field defects was noted

Patients complaints of adverse side effects varied both in frequency and se The pilocarpine treated patients showed a higher incidence of complaints due to myopia and miosis One timolol treated patient was observed subconjunctival haemorrhage However none of the adverse effects were s nor did they cause discontinuation of the therapy

The pulse rate showed a minimal but significant reduction from 75 4 ± 71 2 ± 2 6 in timolol treated patients while systemic blood pressure was influenced

Discussion

study comparing pilocarpine and timolol in various concentrations timolol d to be at least as effective as pilocarpine in reducing an elevated IOP 67% in nolol group and 56% in the pilocarpine group were controlled on topical ient alone Similar results have previously been reported by other authors off 1978 Boger et al 1978 Plane et al 1978 Radius et al 1978 Airaksinen Schiffer 1979)

ording to Zimmerman & Kaufman 1977b the IOP reducing capacity persists t 24 h The long lasting effect of timolol was also demonstrated in this study 17 patients were controlled on once a day regime 10 of them on the lowest ntration (0 25%) The increase of therapy to twice a day administration only ited another 3 patients Several authors (Moss et al 1978 Plane et al 1978 ag et al 1979) have also used the 0 25% concentration but administered it a day It is remarkable that 50% of the IOPs controlled by topical timolol were ited on 0 25% once a day Maybe for some patients a reduction of their it timolol dose would not increase their IOP but diminish the risk of drug side s Furthermore a once a day regime is the most convenient therapy for the it

additive hypotensive effect of acetazolamide to timolol has been described by n (1978) Bischoff (1978) and Keates (1979) In this study the additive ire lowering effect was equivalent in both the timolol and pilocarpine group is a little astonishing as acetazolamide decreases the production of aqueous r (Friedenwald 1949 Becker 1954) a mechanism which is also attributed to l (Coakes & Brubacker 1978 Yablonski et al 1978 Dausch et al 1979) Can educed aqueous in flow interfere detrimentally with the normal physiology of ens cornea and trabecular meshwork? Long term investigation may be sary to evaluate this

nolol like other β-adrenergic blocking agents affects systemic blood pressure ardiac regulation According to Alvan et al (1980) only a small amount of ol 0-5 ng/ml is found in the plasma during topical treatment with 0 5% twice a However this amount seems to be sufficient to effect cardiac regulations as a but significant decrease in pulse rate was observed in this study Whether this ase is sufficient to interfere with the nutrition of the optic nerve is not known fect on blood pressure was noted Neither were any adverse systemic reactions orted by Britman (1979) or Jones & Ekberg (1979) noticed by us

wo timolol and one pilocarpine treated patients regulated at the controls some ess in preexisting visual field defects was noted No certain conclusions can be 1 as the follow up time is rather short but long term studies are in progress

Acknowledgement

Timolol maleate was kindly supplied by Merck Sharpe & Dohme

References

Airaksinen P J (1979) The long term hypotensive effect of timolol maleate comp… the effect of pilocarpine in simple and capsular glaucoma. Acta ophthal. Kbh 57 …

Alvan G Calissendorff B M Seideman P Widmark K & Widmark G (1980) … ocular timolol Clin Pharmacokin 5 95–100

Becker B (1954) Decrease in intraocular pressure in man by a carbonic anhydrase … Diamox Amer J Ophthal 37 13–15

Bischoff P (1978) Erfahrungen mit Timolol in der Glaukom therapie Kl… 173 202–207

Boger III W P Steinert R F Puliafito C A & Langston D P (19…) … comparing timolol ophthalmic solution to pilocarpine in open angle glauco… Ophthal 86 8–18

Britman N A (1979) Cardiac effects of topical timolol New Eng J Med 366.

Coakes R L & Brubaker R F (1978) The mechanism of timolol in low… pressure In the normal eye Arch Ophthal (Chicago) 96 2045–2048

Dausch D Michelson W & Lorenz E D (1979) Die Langzeitbehandlung des … glaukoms mit Timolol Klin Mbl Augenheilk 174 127–135

Diamond G R Werblin T P Richter R Radius R Pollack I P & Maumenee A … Extended clinical studies using timolol in patients with ocular hypertension a… open angle glaucoma Glaucoma I 63–68

Friedenwald J S (1949) The formation of intraocular fluid Amer J Ophthal 3… 9 …

Jones F L & Ekberg N L (1979) Exacerbation of asthma by timolol New Eng J Med

Katz I M (1978) Treatment of chronic open angle glaucoma with timolol maleate … mic solution Efficacy and safety of long term maintenance pp 9–140 Proc … Glaucoma XXIII Int Congr Ophthal Kyoto Japan

Katz I M Hubbard W A Getson A J & Gould A L (19 6) Intraocular pressure … in normal volunteers following timolol ophthalmic solution In… est. Ophthal 15 …

Keates E U (1979) Evaluation of timolol maleate combination therapy in chronic o… glaucoma Amer J Ophthal 88 565–571

Moss A P Ritch R Hargett N A Kohn A N Smith JrH & Podos S M … comparison of the effects of timolol and epinephrine on intraocular pressure … Ophthal 86 489–495

Nielsen N V (1978) Timolol Hypotensive effect used alone and in combin… treatment of increased intraocular pressure Acta ophthal (Kbh) 56 504–509

Plane C Sole P Ourgaud A G Hamard H & Vidal R (1978) Double-observer … of timolol maleate and pilocarpine in open angle glaucoma pp 41–43 P… Glaucoma XXIII Int Cong Ophthal Kyoto Japan

Radius R L Diamond G R Pollack I P & Langham M E (1978) Timolol A new … management of chronic simple glaucoma Arch Ophthal (Chicago) 96 1003–1008

Schiffer H P (1979) Vergleich zwischen Timolol und Pilocarpin bei der Behan… Weitwinkelglaukoms Klin Mbl Augenheilk 175 91–94

Sonntag J R Brindley C O Shields M B Arafat N I Phelps C D (19…) Ti… epinephrine Comparison of efficacy and side effects Arch Ophthal (Chicago) 9…

hi M E Zimmerman T J Waltman S R & Becker B (1978) A fluorophotometric of the effect of topical timolol on aqueous humor dynamics *Exp Eye Res* 27 14?

rman T J & Kaufman H E (1977a) Timolol A new beta adrenergic blocking agent ie treatment of glaucoma *Arch Ophthal (Chicago)* 95 601 604

rman T J & Kaufman H E (1977b) Timolol Dose response and duration of action *Ophthal (Chicago)* 95 605–607

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THE EFFECT OF MELPERON ON OCULAR READAPTATION TIME AS ASSESSED BY A NEW RECORDING TECHN QUE

BY

H BERGMAN[1] S BORG[1] B HÖGMAN[2] H LARSSON and B TENGROTH

A new s mpl f ed techn q e record ng readapta on time af er ph o stress RAT s described The psychometric propert es n terms of n ernal con stency and retest reliab l ty were tested and the effect on RAT af er ntake of melperon at two d fferent dose le els was n e t ga ed and orrela ed to blood plasma levels The results show that there was a sat factory on istency of RAT at each occas on but stab l ty o er a 1 mor h period could not be demonstrated S gn f cant dose dependent changes were recorded af e ntake of melperon but the prolongation of RAT was not s gn f cantl orr lated to blood plasma levels

Key wo d nystagmus central ner o s system drug effects

Registration of readaptation time following a brief exposure to gla e has shown to be a sensitive method of registering the depress e effects of alcol oxazepam respectively on the central nervous system of man (Hogman et al Bergman et al 1979)

In the present study the psychometric properties in terms of n ernal cons and retest reliability of a new simpl fied record ng techn que for RAT wa (Experiment I) In Experiment II the effect on RAT of melperon (Buronil® different dose levels was investigated and correlated to plasma le els of me pe

Rece ed O tober 9 1979

Method of Recording Readaptation Time

ıtation tıme RAT was determıned by regısterıng the pause ın optokınetıc nus OKN that appaears after photo stress on the human eye method for RAT regıstratıon has been presented elsewhere (Tengroth et al

ıaratus used ın thıs experıment ıs a modıfıcatıon of the earlıer vers on A schematıc of ıp ıs shown ın Fig 1 The subject ıs placed ın front of a whıte paınted sphercal screen ıameter of 50 cm The flash lamp and the OKN stımulus projector are placed abo e jects head *The flash lamp ıs an ordınary photo flash (Sunpak GX 24 colour* ıture 6500 K pulse tıme 0 7 ms and pulse energy approx 25 Ws) The lıght flash er 180 of the vısual field) ıs reduced 100 tımes to the lumınance of 10⁴ cdm ² It ıs l from the screen and glares the subject. The OKN stımulus ıs generated by a lamp ıded by a rotatıng drum wıth black and whıte strıpes The stımulus (coverıng a tal area of 25 and a vertıcal area of 10 of the vısual field) ıs projected on the screen ınate accommodatıon the subject wears glasses wıth lenses of +4 dıoptrıes The tal movement of the stımulus can be varıed from 0 to 360° sec The optımum velocıty useful optokınetıc nystagmus varıes from subject to subject but ıs ın the neıghbour

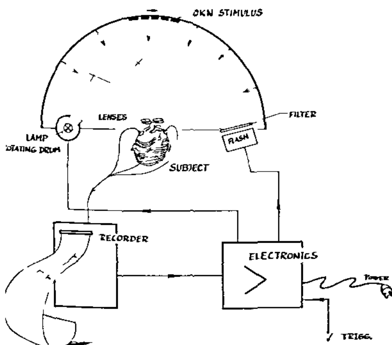


Fig 1
The modıf ed equ pment for determınatıon of readaptatıon tıme (RAT)

hood of 10 /sec The luminance of the OKN stimulus is 10^{-4} cdm ^{2} (scotopic lev... movements are transduced by EOG electrodes to an electrical signal of about ... are recorded by a Siemens Mingograph The signal is amplified and via the elect... to trigger the flash lamp to make it flash only when the subject s eyes a e directed ... ahead The electronics also control the stimulus direction and velocity the level of the signal and the flash

The subject is dark adapted during 5 min before measuring the readaptation ... When this adaptation has taken place 5 RAT registrations are made at one minute ...

In the further analysis of the data the mean of the five measurements is calculated

Experiment I

Subjects and statistical analysis

Thirty healthy volunteer undergraduate psychology students 24 women ... men served as subjects Their mean age was 29 6 years (SD 8 7) None of the... taken drugs for at least two weeks prior to the test sessions Each subject ... investigated twice at the same time of day at an interval of one month.

To investigate the repeatability of the RAT registrations the consistency ... individual s RAT on one and the same day as well as the test retest stability ... longer time period were assessed Thus the internal consistency reliability of ... for both occasions was estimated by calculating *Cronbach* Alpha coef... (Cronbach 1951) High intercorrelations between registrations result in high ... coefficients The retest stability for each series was estimated by ... product moment correlations between results at the two occasions Further ... changes in mean RAT between occasions were tested for significance by St... *t* test for correlated samples

Results

Table I presents retest and internal consistency reliabilities of RAT The Cr... Alpha coefficients were 0 96 and 0 89 respectively for each occasion, ...

Table I

Product moment correlations between occasions mean values (M) standard deviations (SD) *T* test for correlated samples (T_{99}) and alpha internal-consistency coefficients

Rat	II	M	SD	T_{99}	Alpha
First occasion (I)	−05	1 5	4 8	0 49 (n.s)	90
Second occasion (II)		15 1	3 2		89

_ı degree of consistency in the registrations for each separate occasion ıer there was no stability over the one month period the product moment ation between the two occasions was −0 05 ns Furthermore there was -statistically significant change in the group means over the 1 month interval) 42 df 29 $P > 0\ 05$)

Experiment II

cts and statistical analysis

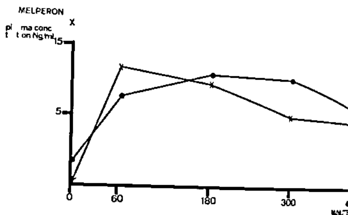
ı healthy male subjects all medical personell of the institutions mean age 29 (SD 2 8) volunteered None of them had consumed drugs for a period of four prior the investigation and smoking was not allowed during the experiment eron was taken per os fasting RAT was recorded at 8 a.m and then diately after intake of respectively 25 and 50 mg melperon per os and ied 60 180 300 and 420 min thereafter

nous blood samples were drawn 60 180 300 and 420 min after drug intake entration of melperon in plasma was estimated by gas liquid chromatography son 1976)

ıe RAT changes at different points of time after the intake of 25 mg and 50 respectively were tested for significance in a two-way analysis of variance m with time after intake as a repeated measures factor Dose level was the een groups factor A trend analysis using orthogonal polynomials was also formed (Winer 1971) In order to obtain the nearest possible equal interval time the following RAT values were included in the analysis RAT 0 RAT 60 180 RAT 300 and RAT 420 In order to assess the relationship between level ıelperon in plasma and RAT the product moment correlation between mean ma level and mean RAT responses for the RAT 60 RAT 180 RAT 300 and T 420 was calculated

ılts

changes in RAT at the above mentioned five points of time after intake of 25 and 50 mg melperon (Buronil®) per os are shown in Fig 2 and the results of the way analysis of variance in Table II There was a statistically significant erence in RAT prolongation between the two dose levels ($P < 0\ 05$) Further e there was a statistically significant change of RAT regardless of dose level (P 01) mainly due to the quadratic component of the trend over time ($P < 0\ 001$) ximum RAT prolongation for the 25 mg group was recorded 3 h after intake l in the 50 mg group 5 h after intake but there was no significant over all



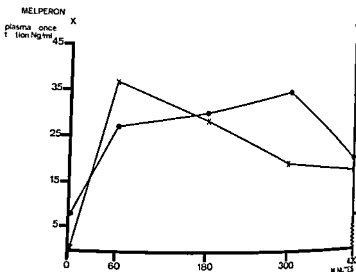


Fig 2

Prolongation of RAT and plasma concentration at different times after intake of 25 (Fig a) and 50 mg (Fig b) per os mean values

interaction between dose levels and change over time ($P > 0.5$) The base l… 0) was not reached during the 7 h period Changes of drug concentr… plasma are shown in Fig 2 for 25 mg and 50 mg respectively For both d… the maximum concentration was recorded 1 h after intake of melper… product moment correlation between the curves of plasma concentration a… recordings based on 5 points of time after drug intake for the two dose l… 0 51 and 0 72 respectively

Table II

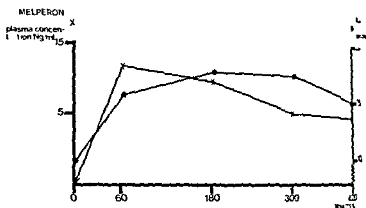
Two-way repeated measures polynomial analysis of variance of RAT at five times after intake of 25 mg and 50 mg melperon per os Source of variation degrees of freedom (df) mean squares (MS) and F test.

Source	df	MS	F
Between subjects			
Dose level (D)	1	1693 4	5 44
Error	10	311 3	
Within subjects			
Times (T)	4	85 1	4 59 *
D × T	4	23 9	1 29
Error	40	18 5	
T (linear)	1	72 2	3 07
D × T (linear)	1	21 9	> 1 00
Error	10	23 5	
T (quadratic)	1	255 7	21 40* *
D × T (quadratic)	1	59 4	5 00*
Error	10	11 9	
T (cubic)	1	6 7	> 1 00
D × T (cubic)	1	0 1	> 1 00
Error	10	20 8	

$P < 0\ 05$ $*P < 0\ 01$ $**P < 0\ 001$

Discussion

first experiment showed that the new equipment used to record RAT had factory psychometric properties in terms of consistency of measurement at 1 occasion However there was no test retest stability The lack of stability over limits the use of RAT registration when making intra individual comparisons nificant changes in RAT were recorded after intake of melperon The prolonga 1 after 50 mg was of the same magnitude as after intake of 20 mg oxazepam per (Bergman et al 1979) Furthermore the RAT prolongation appeared to be e-correlated In a similar experiment intake of 25 mg and 50 mg melperon per was found to significantly influence critical flicker fusion in a dose-dependent hion (Molander & Duvhok 1976) Furthermore the maximum effect on critical ker fusion was recorded after approx 3 h (ibid) The maximum effect of lperon in this study was found to occur after 3 5 h and the effect could still be



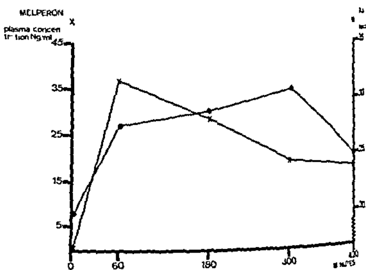


Fig 2
Prolongation of RAT and plasma concentr ation at different times after intake of
25 (Fig a) and 50 mg (Fig b) per os mean values.

interaction between dose levels and change over time ($P > 0.5$) The base line
0) was not reached during the 7 h period Changes of drug concentration
plasma are shown in Fig 2 for 25 mg and 50 mg respectively For both dose
the maximum concentration was recorded 1 h after intake of melperon
product moment correlation between the curves of plasma concentration and
recordings based on 5 points of time after drug intake for the two dose levels
0 51 and 0 72 respectively

D part nent f Ophtl al nology (Hea l E L ner) L er ts f Go henb g and N t o al D fe ce Re ea h In t te St kholm, S den

IPUTER DENSITOMETRY OF RETINAL NERVE FIBRE ATROPHY

A pilot study

BY

MATS LUNDSTRÖM and JAN-OLOF EKLUNDH

La k of nerve f b e layer opacity and a granular appearance of the ret na are mportant funduscop c s gns n opt c atrophy In th s p lot study serially obtained fundus photographs from a case with de elop ng opt c atrophy were subjected to computer dens tometry A monoton c ncrease n local den ty ariations was found during evolut on of optic atrophy The change n dens v ariat ons closely followed the funduscop c change in nerve f bre layer opac ty This method makes t poss ble to detect and quantify d ffuse atrophy of the retinal nerve f b e la er

Key w d op c atrophy ophthalmoscopy fundus pho ography image p ocess ng dens tometry

duscop c defects of the retinal nerve fibre layer have been reported in several ases (see Lundstrom 1977 a recent review) Such defects may be focal or use Focal defects are often prom nent due to the abrupt change in colour at the der between atroph c and normal retina D ffuse atrophy on the other hand h stable and slo ly advancing is difficult to recognize Lundstrom & Frisen ̄5) described the dynamic evolut on of nerve f bre atrophy in a case with amatic les on of the anterior visual pathway Two major types of changes were n during the evolution of atrophy a successive decrease n the nerve f bre layer acity and a successive loss of the striated pattern The decrease of nerve f bre er opacity and the simultaneous increase of retinal m ttling appeared in ck and wh te fundus photographs as an increase of local grey level variations

cei ed October 5th 19 9

Grey level variations in black and white negatives can be recorded ... sitometry as density variations This report describes a method capable of ... and quantifying density variations in black and white negative film The ... presented here are obtained from fundus photographs of the nasal retina ... eye

Materials and Methods

In attempted suicide a 35 years old man received a bullet injury to the right ... knee of the optic chiasm There was an immediate and permanent visual loss ... right eye and an upper temporal field defect in the left eye The evolution ... peripapillary nerve fibre atrophy in the blind right eye was followed by ... ophthalmoscopy and fundus photography Full clinical and technical details ... given by Lundstrom & Frisen (1975) From the series of black and white ... one set of negatives representing different stages of atrophy were selected ... computer evaluation Only negatives showing the optic disc and the nasal peripapil- lary retina were chosen because they showed the best uniformity in sharpness ... centering The sharpest negative from days 25 30 33 40 and 4. after the ... were chosen for study The negatives were scanned by a Ferranti ... scanner in a 512 × 768 raster corresponding to a linear resolution of ab... lines/mm The effective number of grey levels was about 40 Because the ... nerve fibres are radially orientated around the optic disc the matrix was ... along circles concentric with the disc In this way density values were recorded ... circles in a digital picture built up by a linear raster In order to keep the ... error low a first order linear approximation was used Resolution along a ... arc thus remained at about 21 lines/mm

The measure of the density variations in the negatives was computed as f...

1 The centre of the optic disc was determined in interaction with the ... From each negative circular sweeps along arcs in the nasal peripapillary retina ... selected The radii of the circles ranged between 2 5 and 4 5 optic disc radii

2 Each arc was represented by a series of values X, (x_1 x ... x_n) corres... ing to the density level along the arc From this series of values the corresp... series of absolute differences between adjacent density values along the arc ... Y ... y_{r-1}) = (/x_1 x / /x_2 x_3/ ... /x_{n-1} x) was computed Y thus represent... amplitudes in the density curve

3 Picture elements overlying major vessels were discarded by exclud... largest y Five to 15% of the elements were left out in this way

4 The arithmetic mean of the remaining y (mean amplitude) was comput... each arc and used as a measure (M) of the local density differences

Results and Discussion

les of original photographs and their digital transforms recreated on film by nning device are given in Fig 1 Examples of the density variation along the are shown in Fig 2

mean amplitude (M) of each arc was computed The values from correspond s in the series of negatives representing different stages of atrophy were red Because the actual values were of little importance we have ranked the rements for each arc The ranking list is shown in Table I As can be seen in I there was a monotonic change in density variation through the series of ves Ophthalmoscopy during the same period of time revealed a successive se in nerve fibre layer opacity This decrease in retinal opacity corresponded increase in local grey level variations in the black and white negatives The led monotonic increase in density variations in the same series of negatives tes that densitometry of fundus photographs may be used to detect changes nerve fibre layer appearance

this pilot study picture processing and densitometry was performed with uter technique This expensive method was used in order to make the ifying easier In the digitization process a scanner with a 40 μm aperture was and the effect of film granularity could therefore be neglected The diameter e nerve fibre bundles in our negatives was estimated to be 90 240 μm efore the linear resolution of the scanner was considered sufficient to record ges in the striated pattern However in the series of negatives there was an asing sharpness of the vessel edges due to the increase in atrophy This change her with the decrease in opacity made a negative to-negative comparison of iency components corresponding to the striated pattern difficult Further nasal to the optic disc the striated pattern was not as prominent as in other of the peripapillary retina By excluding five to 15% of the largest density tions the effect of retinal vessels and striations was diminished and changes in almottling and opacity were enhanced The actual % chosen in the interval was ritical Being radially distributed the nerve fibre bundles were examined on s concentric with the optic disc Circles with a radius of 2 5 to 4 5 times the us of the optic disc were used When a larger radius was used the characteristic ormits disappeared This agrees with the ophthalmoscopic finding of decreased ility of the nerve fibre layer at this distance from the optic disc Conversely by the optic disc abundant reflexes from the internal limiting membrane and local variations in background pigmentation impaired definition of the nerve e layer The effect of other structures e g retinal blood vessels and choroidal uls were eliminated by excluding the largest density variations The computer minated the more extended variations in contrast between different negatives

B









A

Fig 1

Pictures from day 25 (A) and 47 (C) respectively and their correspond[illegible] (B+D) The matrix was sampled along arcs concentric with the optic disc shown [illegible] pictures (B+D)

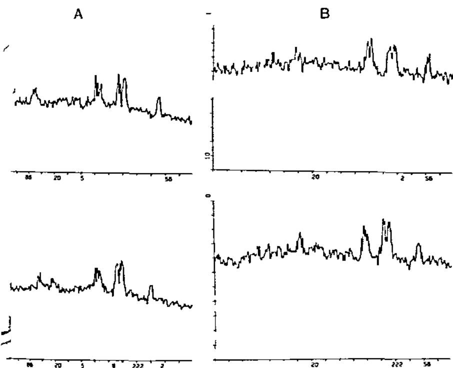


Fig 2

tometry curves from the pictures shown in Fig 1 The curves represent density values along two arcs on day 25 (A) and the same arcs on day 47 (B)

Table I

ing of the negatives The negatives are identified by the number of days passed after the The radius is expressed as a multiple of the radius of the disc Lowest ranking number (1) indicates the lowest mean amplitude

egative days)	Radius														
	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
25	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
30	2	2	2	2	3	2	3	2	3	2	2	2	2	2	2
33	4	3	3	3	2	3	2	3	2	3	3	3 5	3	3	3
40	3	5	5	4	4		4	4	5	4	4 5	3 5	4		4
4		4	4	5	5	4		5	4	5	4 5	5	5	4	5

caused by exposure variations The sharpness of the negatives ou ht ha s point because in blurred negatives the grey level variations decrease and ... the density variations Therefore a set of slightly blurred ne... was examined Still a monotonic increase in density variations was f..d ... pronounced than when sharp negatives were examined The eye grou.d ... is extremely difficult to reproduce in photographs taken at differ... According to Behrendt & Doyle (1965) differences of centering on the e... may cause errors up to 10% in image size Moreover centering of the ... not exact Considering the series of negatives the increasing atrophy coul... established from one circle alone per picture due to geometrical errors ... circles were however sufficient

In this case of traumatic optic atrophy the changes in the retinal nerve ... were due to a more or less simultaneous degeneration of all retinal nerve ... Therefore these findings can not be directly transferred to stu... progressive loss of single nerve fibres or bundles of nerve fibres as in ... This pilot study shows however that it is possible to detect and quant... atrophy of the retinal nerve fibre layer Similar findings in atrophy of p... macular bundles have been reported by Tagami (1979)

Acknowledgments

The authors wish to express their gratitude to professor Bjorn Tengroth f... gener...

References

Behrendt T & Doyle K (1965) Reliability of image size measurements ... the ... fundus camera Amer J Ophthal 59 896–899

Lundstrom M (1977) Optic atrophy in compression of the chiasm A funda... the human retinal nerve fibre layer Thesis University of Gothenburg

Lundstrom M & Frisen L (1975) Evolution of descending optic atrophy A case rep... ophthal (Kbh) 53 738–746

Tagami Y (1979) Correlations between atrophy of maculopapillar bundles and functions in cases of optic neuropathies Doc ... Ophthal Proc Ser 19 ...

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A DEFECT IN THE BLOOD RETINA BARRIER IN THE OPTIC NERVE HEAD REGION IN THE RABBIT AND THE MONKEY

BY

TOR FLAGE

The permeabil ty propert es of the t ssues in the opt c nerve head region have been n est gated n monkey and rabb t us ng horserad sh perox dase as an h stochem cal tracer Follo ng intra enous adm n stration the tracer d ffused from the per pap llary cl oro d nto the d fferent parts of the opt c nerve head reg on and also nto the receptor layer of the sensory retina adjacent to Kuhnt n ermed ary tissue Th s observat on demonstrates a defect in the blood ret na barrier n th s reg on The defect in the permeab l ty barr er s most l kely located e ther to the ret nal p gment ep thel um near the opt c nerve head to the Kuhnt intermed ary t ssue or to the junct on between these t s ues

Key wo ds blood ret na barrier defect rabb t monkey horserad sh perox dase optic nerve head ultrastructure

blood retina barriers play an important role in the present concept of retinal ology It is generally accepted that the endothelium of the retinal vessels and retinal p gment epithelium (RPE) form the anatomical basis for the barriers cells n these tissue layers are interconnected by tight junctions Peyman & Bok 9) demonstrated the blood retina barriers n the primate retina using horse sh peroxidase as a prote n tracer In experiments using this tracer we stud ed permeab l ty properties of the tissues in the opt c nerve head region in rabbit monkey and found that horseradish peroxidase diffused from the peripapillary ro d into the optic nerve tissue proper thus demonstrat ng a defect in the

ed January 15 1980

blood optic nerve barrier (Flage 1977) In the same study the tracer was observed in the peripapillary sensory retina indicating a defect in the b[illegible] barrier in this region In the present article this observation will be [illegible] greater detail

Material and Methods

The material and the procedures have previously been described (Flage 1[illegible] from 15 rabbits and 4 monkeys (Cercopithecus aethiops) were examined in [illegible] Horseradish peroxidase (HRP) Sigma type II molecular weight approximately [illegible] daltons molecular diameter of about 4 5 nm was used as an histochemical tracer [illegible] was administered by intravenous injection The amount of tracer used for the [illegible] 100 mg/kg body weight For the rabbits the amount varied between [illegible] weight The time from the injection of the tracer until the enucleated eye was [illegible] cooled fixative called the exposure time to HRP ranged from [illegible] The same period in the monkeys varied between 20 and 60 min The tissues were [illegible] by light microscopy either in 5 15 µm sections obtained on a freezing microtome [illegible] thick sections either unstained or following staining with toluidine blue [illegible] were examined in a Siemens Elmiskop 1A unstained or stained with [illegible] alkaline lead

Results

Following intravenous injection HRP leaked out of the choroidal capillaries [illegible] the peripapillary choroid the tracer spred into the tissues of the optic nerve [illegible] region of rabbit and monkey in a distinct pattern The details of this pattern [illegible] been described elsewhere (Flage 1975 1977) Bruch membrane the border [illegible] of Elschnig and small islands of connective tissue in Kuhnt intermediary [illegible] (KIT) were heavily stained by the tracer

The most striking observation in the present context was the finding of [illegible] the peripapillary sensory retina (Fig 1) This finding was also present in the eyes initially fixated by perfusion In the rabbit eyes with exposure time to HRP [illegible] than 10 min the tracer was not regularly present in the peripapillary retina [illegible] monkey eyes the staining caused by the tracer in the retina was generally less [illegible] than in the rabbit eyes

In the sensory retina HRP was located in the subretinal space and between outer and inner segments of the visual cells No staining was present in the [illegible] retinal layers The HRP stained peripapillary sensory retina and subretinal [illegible]



Fig 1

nerve head region in rabbit following intravenous injection of horseradish peroxidase black staining marks the prescence of the tracer Small arrows point to the tracer in the papillary sensory retina No staining is present in the inner retinal layers except in the ular connective tissue Long arrow points to Kuhnt intermediary tissue The border f Elschnig (E) is heavily stained by the tracer which has also spread into the adjacent optic nerve tissue (ON) X 300

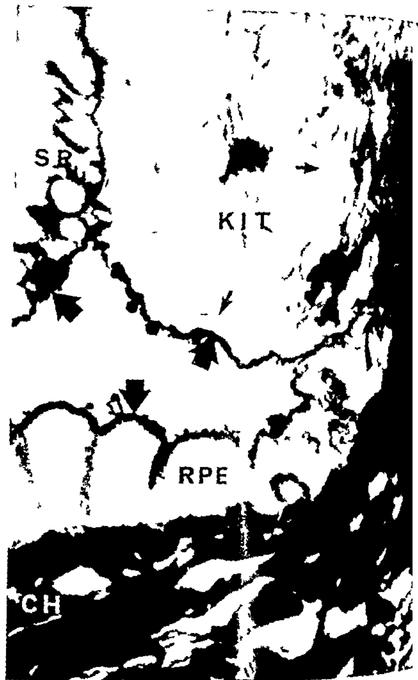


Fig. 2

Part of Fig. 1 in higher magnification showing the relationship between the choroid (CH), border tissue of Elschnig (E), the retinal pigment epithelium (RPE), Kuhnt [illegible] tissue (KIT) and sensory retina (SR). Small arrows point to tracer in the [illegible] KIT. Broad arrows point to tracer lining the subretinal space. The [illegible] junction between the last RPE cell and a glial cell × [illegible]



Fig 3

on micrograph monkey optic nerve head region Broad arrows point to Bruch mbrane and connective tissue in Kuhnt intermediary tissue (KIT) stained by horseradish roxidase Open arrows mark the tracer between the glial cells of KIT Arched arrows point tracer in the subretinal space Optic nerve (ON) Retinal pigment epithelium (RPE) Inner segment of visual cell (IS) Uranyl and lead X 4280



Fig 2

Part of Fig 1 in higher magnification showing the relation hip between the border tiss e of Elschnig (E) the retinal pigment epithelium (RPE) k tissue (KIT) and sensory retina (SR) Small ar ows point o tracer in he KIT Broad arro s point to tracer l n ng the subretinal pa e The a hed ar junction be een the last RPE cell and a glial cel

defect in the blood retina barrier is most likely located either to the RPE near tic nerve head to the KIT or to the junction between these tissues
se possible routes of diffusion will be the subject of further investigation & Ringvold 1980)

Acknowledgment

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References

T (1975) The distribution of intra enously administered peroxidase in the optic nerve ad of rabbit and monkey Acta phthal (Kbh.) 53 801–808
T (19 7) Permeability properties of the tissues in the optic nerve head region in the bit and the monkey Acta phthal (Kbh) 55 652 664
T & Ringvold A (1980) Demonstration of a diffusional pathwa between the bretinal space and the juxtapapillary tissue An in itro experiment using horseradish roxidase as a tracer In preparation
tami S Ohkuma M & Tsukahara I (1976) Kuhnt intermediary tissue as a barrier tween the optic nerve and retina Albr ht G aef Arch kl n exp Ophthal 201 57 67
nan G A & Bok D (1979) Peroxidase diffusion n the normal and lasercoagulated mate retina In v t Ophthal 11 35–45
M O M Shih C Y & McLean I W (1975) Is there a blood-brain barrier at the optic e head A ch Ophthal (Chicago) 93 815–825
kahara I & Yamashita H (1975) An electron microscopic stud on the blood-optic nerve nd fluid-optic nerve barrier Albrecht v C aef Arch klin exp Ophthal 196 239–246

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EVIDENCE THAT HYPOTONY IN RETINAL DETACHMENT IS DUE TO SUBRETINAL JUXTAPAPILLARY FLUID Drain...

BY

AMUND RINGVOLD

One case of aphakic retinal detachment with increased intraocular pressure is described. Overnight the intraocular pressure fell abruptly to non measurable values and simultaneously the detachment had advanced to the optic disc border. The hypothesis is formulated that decreased intraocular pressure in eyes with retinal detachment is brought about because intraocular fluid is leaking out of the eye through a subretinal route to the peripapillary tissue. Additional support for this posterior aqueous outflow is obtained from clinical studies showing that maximum hypotony is reached when the detachment has advanced to the optic disc border.

Key words: retinal detachment – intraocular pressure – outflow fac... glaucoma

Since Graefe in 1869 (see Leber 1916) considered the intraocular pressure to be normal or lower in eyes with retinal detachment, this observation has been confirmed both before and after the introduction of tonometry (see D... 1967). The search for the cause of this IOP decrease has also given rise to reports with conclusions roughly falling into two groups. Some authors a... there must be an increased outflow in such eyes, perhaps because of subret... absorption by the choriocapillaris (Leber 1916, Kleiner 1933), whereas investigations lend support to the view that the IOP is low because aqueous is reduced in eyes with detached retina (Becker 1963, Dobbie 1963, Ro... Regan 1965, Regan & Rousseau 1966, Syrdalen 1970).

The present study is an attempt to analyze aqueous humour dynamics with retinal detachment. On account of observations in one case of ...

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ment and a clinical material of retinal detachment the hypothesis is put d that the IOP decrease in eyes with retinal detachment may be due to apillary drainage of subretinal fluid

Case Report

ar-old myopic woman had successful intracapsular cataract extraction on the right eye esulting visual acuity of 5/5 (+3 sph) Eight months later she underwent cataract ion on her left eye with postoperative visual acuity of 5 / (+2 sph) During the last ion there was considerable vitreous protrusion after lens extraction and although no is loss occurred corneal suturation was impeded by itreous substance in the anterior er

weeks after cataract extraction on the left eye the patient came to the hospital with a history of visual loss on this eye and periodic frontal headache on the same side The nation revealed that the right eye was unchanged from the description abo e The IOP 9 mm by applanation tonometry and this eye remained normotensi e during the ing observation period

he left eye which also showed normal aphakic anterior chamber depth the ruptured us face was perforated by some thin vitreous threads protruding into the anterior ber Gonioscopy revealed some gonio-synechies in the upper nasal quadrant and gh the peripheral coloboma a vitreous connection was attached to the corneal scar otherwise appeared regular A low retinal detachment with two pre-equatorial breaks temporal half was present involving the macula and co ering the 4 12 o clock area The nor limit reached to one disc diameter from the optic nerve (Fig 1a) The visual acuity inger counting 2 3 m and IOP was 42 mm Despite 500 mg acetazolamide per os and drop of timolol maleate (Blocadren 0 5%) in the left eye the IOP was st ll 37 mm 2 h

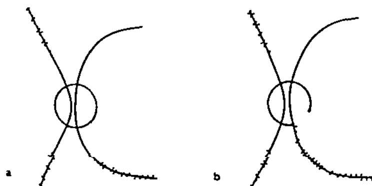


Fig 1

ematic drawing of the left fundus with the retinal detachment (drotted area) and its tion to the optic disc a) as IOP was 42 mm and b) as IOP was extremely low (not asurable) next morning Note the detachment reaches the disc border in the 4-6 o clock region in Fig b

later The next morning however the anterior chamber was deep the IOP [illegible] extreme hypotony giving a zero value by applanation tonometry and the [illegible] drugs were promptly stopped At this time a striking change was observed in [illegible] area as the detachment now had advanced to the disc border in the [illegible] a marked tunnel shaped retinal elevation (Fig 1b) Otherwise the fundus appeared [illegible] evening before The eye was operated with encircling band local [illegible] cryopexy and drainage of subretinal fluid The next morning the IOP was 10 [illegible]

Material and Methods

In order to determine the relationship between the detachment-disc distance [illegible] the size of the detachment in conventional rhegmatogenous detachments [illegible] schematic fundus drawings of such patients admitted to the Eye Department [illegible] Rikshospitalet in 1976 were reviewed The drawings had been made by [illegible] skilled ophthalmologists after clinical examination with indirect ophthalmoscopy [illegible] and with a three mirror Goldmann lens All eyes included in the material [illegible] primary retinal detachment and there had been no previous surgery [illegible] ophthalmic disease A total of 128 detachments were used In those cases [illegible] detachment did not touch the disc border the shortest distance (called a [illegible] the posterior detachment border and the optic disc was measured Subsequently [illegible] detachments were cut out with a pair of scissors weighed and the size [illegible] detached area was then calculated in % comparing its weight to the weight [illegible] fundus area

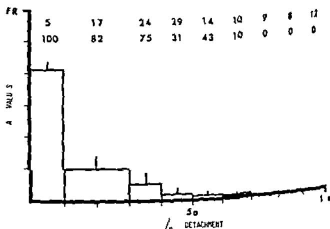


Fig 2

The curve shows the relationship between detached area in % of total fundus [illegible] abscissa and its corresponding distance *a* to the optic disc along the ordinate [illegible] distance between detachment and optic disc FR = fundus radius of the [illegible] distance representing the greatest possible *a* value Number of cases in each [illegible] indicated in the upper line whereas the lower line shows in % how many [illegible] respective groups that did not reach the disc

Results

elationship between the distance a and the size of the detached area is seen in

Discussion

occurrence of acute hypotony combined with deep anterior chamber in eyes retinal detachment similar to the present case was first described by Schnabel) and later it has been observed by several authors (see Beigelman 1929) As narized by the last one different mechanisms have been made responsible for phenomenon However the coincidence of an abrupt fall in IOP as the hment reached the disc through the tunnel shaped extension indicates that tony in this case was due to leakage of subretinal fluid along the optic nerve interpretation is supported by the fact that the IOP was again raised from measurable values in the pre-operative phase to 10 mm on the first day after ure of retinal breaks with the buckling procedure

ompared to the conventional rhegmatogenous retinal detachment with mote hypotony in the pre-operative stage the refered case was unusual in showing ased IOP on arrival at the hospital This was probably due to changes in the ecular meshwork secondary to cataract extraction and accordingly it is sug ed that there was nothing unusual with the detachment itself The syndrome of e hypotony may therefore represent an exaggerated state of the frequently ring moderate hypotony in eyes with retinal detachment

he second part of this study was performed to test whether the hypotony in eyes conventional retinal detachment may be brought about because intraocular d seeps through the retinal breaks leaving the eye through a subretinal route to connective tissue around the optic nerve as visualized in Fig 3 This flow would t substantial resistance first in that part of the subretinal space where the retina ttached to the pigment epithelium i e along the route defined as the shortest ance (a) between the detachment and the disc Accordingly the degree of otony would be inversely proportional to the distance a It should be stressed t when a is zero and the detachment thus has reached the disc the IOP would decrease any more even if the detachment continues to increase Consequently ximum hypotony should be achieved at the moment the detachment reaches the ic disc To test the validity of the hypothesis it seems therefore essential to wer the following two questions 1) How large is the detachment when it just ches the optic disc? 2) At what detachment size is maximum hypotony reached?

As to the first question Fig 2 shows that roughly 40-70% is detached as it reaches optic disc.

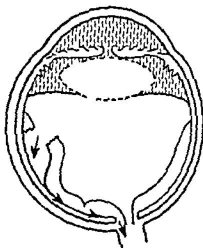


Fig 3

Arrows indicate the suggested posterior outflow pathway of the intraocular fluid ... subretinal space to the juxtapapillary tissue in eyes with retinal detachment

In order to answer the second question data from the Syrdalen (19.. (1933) and Dobbie (1963) investigations are adapted to graphs by the author in Figs 4 and 5 respectively Because the degree of hypotony ... influenced by the age of the detachment (Syrdalen 1970) Fig 4 presents ... based on the total material and one graph with data derived from the 1-... detachments It is seen in Figs 4 and 5 that maximum hypotony is present ... range from below 50% to 66% detachment which is the same interval ... the size of detachments are falling when they just reach the disc (comp. Fig ... coincidence speaks in favour of the presented hypothesis

Interestingly a subretinal defect in the blood retina barrier has been ... next to the optic nerve (Flage 1980) and more directly this opening ... demonstrated in in vitro experiments by showing free diffusion of ... horseradish peroxidase into the connective tissue surrounding the optic ... (Flage & Ringvold 1981)

As stated above according to the hypothesis the degree of hypotony should ... inversely proportional to the distance a However since the interstitial ... between the external limiting membrane and the pigment epithelium ... soluble in saline (Berman 1969) it seems reasonable that this substance ... changed or even to some extent washed out through the flow In other ... flow is increasing when the distance a becomes shorter there should ... decreasing subretinal flow resistance per length unit along the distance a ...

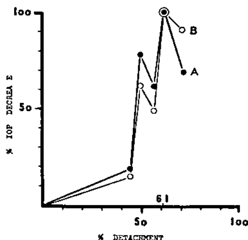


Fig 4

s obtained after statistical calculations of the material presented by Syrdalen (19 0 p The five points along the abscissa are found by calculating mean values from those achment numbers lying closely together Curve A includes the total material as mean of the following groups (44 04–44 33) (49 06–49 33) (55 34–55 94) (60 5–60 94–61 0) –69 ,6–70 2 70 9–74 86) Curve B represents numbers from the first 14 days only 1–44 33) (49 06–49 33) (55 34–55 94) (60 94–61 0) (69 76) The corresponding mean lifferences are seen along the ordinate In both curves the greatest IOP difference was set to 100%

sted to be one reason why small detachments do not alter the tension ficantly as pointed out by Dobbie (1963) and seen in Figs 4 and 5

the case that the hypotony in retinal detachment is due to subretinal ipapillary fluid drainage tonography seems unsuitable to examine the aqueous mics in such eyes because the extrabulbar counterpressure induced at the erior pole through the weight of the tonometer is likely to impair this posterior low

References

ker B in Discussion of Smith J L (1965) Retinal detachment and glaucoma. *Trans Amer od. Ophthal Otolaryng* 67 731–732

gelman M N (1959) Acute hypotony in retinal detachment *Arch Ophthal (Chicago)* 1 53–467

man E. R. (1969) Mucopolysaccharides (Glycosaminoglycans) of the retina Identification istribution and possible biological role *Mod P b Ophthal.* 8 5–31

bie J G (1963) A study of the intraocular fluid dynamics in retinal detachment *Arch phthal. (Chicago)* 69 159–164

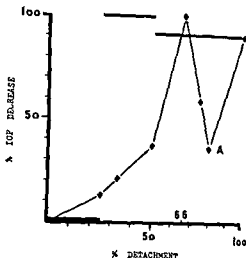


Fig 5

Curve A represents the material presented by Kleiner (1933 p 4?9 ?00 The p based on mean values of the respective groups of %-detachment and their corresp mean IOP differences Dobbie's material (1963 p 160–161) shows IOP values detachments smaller than 25% larger than 50% and the region in between indicated as thick lines In both investigations the greatest IOP difference was se

Duke Elder S (1967) System of Ophthalmology vol X Diseases of the retina p Kimpton London

Flage T (1980) A defect in the blood retina barrier in the optic nerve head rabbit and the monkey *Acta ophthal (Kbh) 58* 646–652

Flage T & Ringvold A (1981) Demonstration of a diffusional pathway between subretinal space and the juxtapapillary tissue An in vitro experiment using horse peroxidase as a tracer *Acta ophthal (Kbh) 59* in press

Kleiner L (1933) Der intraokulare Druck bei Netzhautablösung ... 485–506

Leber Th (1916) In Graefe Saemisch Hess Handbuch der gesamten Augenheilkunde 1416–1428 Bd VII/2 Wilhelm Engelmann Verlag Leipzig

Regan C D J & Rousseau A P (1966) The intraocular dynamics of eyes ... detachment *Amer J Ophthal 61* 696–702

Rouseau A P & Regan C D J (1965) Pressure cup studies in eyes with retinal ... *Arch Ophthal (Chicago) 73* 803–809

Schnabel J (1876) Über Glaucom und Iridectomie *Arch Augen und Ohrenheilk*

Syrdalen P (1970) Intraocular pressure and ocular rigidity in patients with retinal detachment I Preoperative study *Acta ophthal (Kbh) 48* 1034–1035

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THE ERG c WAVE IN VITELLIRUPTIVE MACULAR DEGENERATION (VMD)

BY

SVEN ERIK G NILSSON and KLAS OLAV SKOOG

Dc ERG registrations and EOG record ngs were obta ned from s x patients w th vitell rupt ve macular degeneration (VMD) In all cases the EOG was h ghly pathological but the *a* and *b*-wa es of the ERG were normal Th s s t p cal of VMD wh ch starts as a general zed defect of the p gment ep thel um Four pat ents showed no evidence of a *c* wave The other pat ents demon strated small *c* waves but only under certa n st mulus cond tions Thus vary ng stimulus durat ons ntens t es and frequencies are somet mes needed to dec de whether or not ERG *c* wa es can be el cited in d fferent diseases or suspected d sorders The find ngs are n agreement with the presence of a general zed p gment ep thelial defect in VMD s nce the major pos tive component of the *c* wa e is generated b the p gment ep thel um receptor complex

Key w d electroret nography cl n cal method *c* wave ret na p gment ep thel um vitelliruptive macular degeneration

e hered tary condition originally described by Best (1905) has since been erred to with a large number of designations We have chosen the term elliruptive macular degeneration (VMD) (Krill et al 1966) This condition has n stud ed extensively both clinically and electrophysiologically Very thorough iews may be found elsewhere (Deutman 1971 Krill 1977) A Swedish pedigree h VMD was described by Barkman (1961) Nordstrom et al (1972) and others As it appears from the highly pathological EOG (Krill et al 1966 Francois 1968 utman 1969) in the presence of normal *a* and *b*-waves of the ERG (Francois et al 63 Krill et al 1966 Francois 1968) VMD starts as a generalized defect in the gment epithelium Structural evidence to this effect is not complete but two cases

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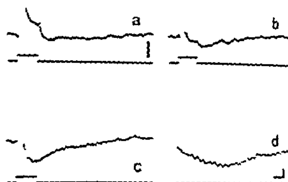


Fig 2

Registrations from a patient (S D) who lacked *c* waves under all [illegible]. Stimulus intensity 3 5 4 5 5 5 and 4 5 rel log units in Figs 2a, 2b 2c and 2d [illegible]. Amplitude calibration 100 μV (the calibration line in Fig 2a also applies to [illegible]). Stimulus duration 1 s in Figs 2a c (indicated on lower lines) Stimulus duration [illegible]. Time calibration 2 s in Fig 2d

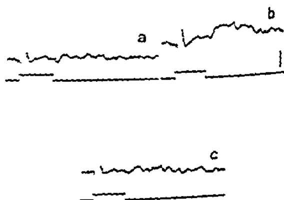


Fig 3

Registrations from a patient (H D) who developed a *c* wave when oscillations of [illegible] amplitude were elicited through repeated stimulations and registrations [illegible] intensity 4 5 rel log units Amplitude calibration 100 μV Stimulus duration [illegible] lower line) Fig 3a from the beginning of the series (average of four recordings) [illegible] min 6-7 (average of four recordings) and Fig 3c from min 10-11 [illegible] recordings)

l of 1 s flashes the trough became very deep and did not reach the iso-electric
til after the end of the stimulus (Fig 2 d)
of the patients (H D and S D) were studied with repeated stimulations and
ations with 1 s flashes at log rel intens 4 5 for 20 min One of them (S D the
patient as in Fig 2) showed a shallow trough (as in Fig 2 b) throughout the
The second patient (H D) in which no c wave was seen at the beginning of
nes (Fig 3a) demonstrated a small but quite clear c wave after 3-4 min It was
nal in amplitude (approximately 120 µV) at 6-7 min (Fig 3b) and from 10
disappeared again (Fig 3c)
the two lowest intensities the so-called d c potential was seen lasting until the
f the stimulus (Figs 1 and 2a) It appeared to be normal
conclusion all six patients lacked normal c waves Four of them (J D S D A
d B S) showed no c wave at all One patient (G D) displayed small c waves
nly at low intensities Another subject (H D) also showed small c waves but
upon repeated registrations which served to provoke c wave amplitude
ations

Discussion

ough there are a few healthy individuals who lack c waves (Taumer 1975
on & Skoog unpublished data) the large majority of subjects have clear
ves. When going from log rel stimulus intensity 3 5 to 5 5 Skoog & Nilsson
4a) obtained a steady increase in c wave amplitude
he small number of patients in the present study does not permit formal
stics However given the scarcity with which the authors and others have
untered normal individuals without c waves it is highly unlikely that the
ecutive appearance of six VMD patients with no or in two cases atypical c waves
coincidence The conclusion seems to be that VMD patients at least those
nging to the Swedish pedigree have no or pathological c waves
n fact our present results in subjects with a diffusely pathological pigment
helium as reflected by abnormal EOG and histology (see introduction) were
ected Such a condition would most likely lead to a decreased P I (slow major
itive component of the c wave originating in the pigment epithelium receptor
mplex) and an intact slow P III (slow negative component of the c wave from the
üller cell receptor complex) (see introduction) The total absence of P I would
d to a deep negative trough (isolated slow P III) instead of a c wave (Noell 1953
d others) Some P I activity would give shallow troughs straight lines or low
aves If hypothetically in a few persons with healthy eyes the slow P III was very
ge one would encounter a low or even absent c wave This is a possible
planation as to why some normal persons seem to lack a c wave

Oscillations of the standing potential (SP) of the eye and amplitude [illegible] the *c* wave occur in a parallel way in man (Nilsson & Skoog 1973). The [illegible] dark trough and light peak in the EOG, reflecting the oscillation of the SP [illegible] changes in illumination, is not equivalent to the presence of a *c* wave [illegible] Central retinal artery occlusion can abolish both oscillations [illegible] affecting the average *c* wave amplitude (Textorius et al. 1978). Thus the [illegible] in itself does not necessarily lead to an anticipation of small *c* waves.

It is particularly interesting to note that one patient (H. D.) with a [illegible] after the fast ERG-potentials, probably reflecting a poor P I function, [illegible] reasonable *c* wave about 4-10 min after the onset of registrations [illegible] roughly in time to the development of the first maximum in the *c* wave [illegible] oscillations in normal subjects (Skoog & Nilsson 1974b). In this patient [illegible] showed some oscillatory ability since the Arden index was 1.70. The SP and [illegible] oscillations are related, and thus it was not wholly unexpected that, by [illegible] the oscillations, small but clear *c* waves could be brought about for some [illegible] patient (S. D.) with no evidence of a *c* wave in spite of the provocative [illegible] registrations/min had a shallow trough to begin with and an Arden index of [illegible] cannot be decided on the basis of this study, whether the cyclic change is [illegible] P I, in P III or in some other slow component, which may take part in the [illegible] up of the *c* wave.

Concerning the patient (G. D.) with *c* waves after weak stimuli only, it is [illegible] to suggest that the condition reflects a failure of the diseased pigment epithelium [illegible] produce more than a small positive P I, even if the stimulus became [illegible] to give rise to a large negative slow P III from the inner, intact retina. The large slow P III would completely bury the small P I.

In conclusion, patients with vitelliruptive macular degeneration (VMD) [illegible] have no or very small *c* waves because of a pigment epithelial dysfunction. As [illegible] out in this small study, varying stimulus conditions must be used in order to [illegible] whether or not *c* waves are present in different diseases or suspected [illegible] should try to elicit oscillations of the *c* wave amplitude by repeated [illegible] registrations. In this way otherwise hidden *c* waves may sometimes be [illegible] pointed out by Textorius et al. (1978) one cannot perform reliable *c* wave [illegible] without taking into account the effect of their amplitude oscillations.

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References

— (190ɔ) Uber e ne hered tare Maculaaffektion Be trage Zur Vererbungsleh e *Z nheilk 13* 199 212

ɔ an Y (1961) A cl n cal study of a cen ral tapetoretınal degenerat on *A ta ophthal (Kbh) ɔ63* 6 1

ıan A F (1969) Electrooculography ın famıl es w th v telliform dys rophy of the fo ea *Ophthal. (Chicago) 81* 30ɔ 316

ıan A F (1971) The Hered tary Dystroph es of the Pos erior Pole of the Eye pp 999 Charles C Thomas Sprıngf eld Ill

ɔus J (1968) V tell form degeneration of the macula *Bull N Y A ad Med 44* 18 9

ɪ ous P Gallet G & Blervacque A (1963) La degenerescence ell forme de la macula *Soc Ophthal Franc 63* 4ɔ0 4ɔ1

— t R (1933) The components of the retınal action potential n mammals and the r ıtion to the discharge n the optıc nerve *J Phys ol Lond.)* 907 939

zsch R (19 9) Some characteristics of slow PIII-components n the ERG of the ısolated ƨerperfused rabb t retına Proc XVIIth ISCEV S mpos *Docum. ophthal P oc Serie* (In ss)

A E (19 7) *Hered tary Retınal and Choro dal D seases Vol II* pp 66ɔ 04 Harper & ɪ w Hagerstown Maryland

A E Morse P A Potts A M & Kl en B A (1966) Hered tary v elliruptı e macular eneration *Amer J Ophthal 61* 140ɔ–141ɔ

on S E G (1980) Electrophys ological responses related to the p gment ep thel um and ın eraction w th the receptor layer *Neurochemistry 1* 69 80

on S E G & Skoog K -O (19 ɔ) Co arıatıon of the stimultaneousl recorded wa e and ..nding potentıal of the human eye *A ta ophthal (Kbh) 53* 91 30

I W K (19ɔ3) Stud es on the Electrophys ology and Metabolism of the Retına. L S A F hool of A ıatıon Med cine Randolph F eld Texas

ds rom S Holmgren G & Tho burn W (1972) A genetıc study of congen tal hered tary acular degeneration ın the county of Vasterbotten Sweden *A ta ophthal Kbh. 50* 9 ɔ49

ley B H (19) Potass um and the photoreceptor dependent p gment ep helıal perpo larızatıon *J gen Phy iol 0* 405 49ɔ

ley B H & Green D G (19 6) Correlation of l ght nduced changes n retınal ıtracellular potass um concen ratıon with c wave of the electroretınogram *J Neu ophys ol 9* III 1133

ıley B H Steınberg R H Miller S S & Nılsson S E G (19) The ın vitro frog p gment p thelial cell hyperpolarization n response to l ght *In e t Ophthal 16* 71 4

og K-O (19 ɔ) The d rectly recorded standing po entıal of the human eye *A ta ophthal Kbh) 53* 190 13?

og K-O & Nılsson S E G (19 4a) The wa e of the human d c registered ERG I A uantıtatı e stud of the relationsh p between c wa e amplı ude and stimulus intens ty *Acta phthal Kbh. 52* ɔ9 3

og K O & N lsson S E G (19 4b) The c wa e of the human d c regıs ered ERG II dic arıatıons of the c wa e ampl tude *A ta ophthal (Kbh. 52* 904–912

ınberg R H Schm dt R & Brown K T (19 0) Intracellular responses to l ght from cat pigment ep thelium orıgın of the electroretınogram c wa e *Natu e 22* 98 30

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CORRELATION OF VISUAL EVOKED POTENTIALS *OPHTHALMOLOGICAL AND NEUROLOGICAL FINDINGS* AFTER UNILATERAL OPTIC NEURITIS

BY

H BYNKE I ROSEN and M SANDBERG WOLLHEIM

'orty-two patients were tested with pattern reversal visual evoked potentials VEPs) 1–8 years after an episode of acute unilateral optic neuritis The umulation was produced by dot as well as checker-board pattern An inexpectedly large proportion (12 cases) showed normal VEP latencies from he affected eye In these patients the initial visual acuity was on the a erage ignificantly better than in cases with prolonged VEP latencies They also had ignificantly fewer remaining ocular signs than the patients with abnormal EPs On the other hand, no correlation was found between the VEP findings ind the incidence of CSF abnormalities multiple sclerosis and HLA types
n 14 patients of which 13 belonged to the group abo e repeated VEP tests vere performed from the acute onset of the disease and up to 2 years ifterwards confirming that a considerable normalization of VEP latencies xcurs

Key words optic neuritis visual evoked potentials (VEP) – pattern reversal umulation – ocular signs CSF abnormalities – multiple sclerosis – HLA types

vious studies of visual evoked potentials (VEPs) after optic neuritis normal es of pattern reversal VEP have been reported very rarely e g in 3–6% of aterials of Halliday et al (1972 and 1973a) and Shahrokhi et al (1978) Also 3 patients with suspected multiple sclerosis and a history of optic neuritis d latencies have been found in few cases (Halliday et al 1973b Asselman et al.

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1975 Matthews et al 1977 Shahrokhi et al 1978) The ultimate visual a[illegible] completely uncorrelated with the VEP latency but it was clearly correlated [illegible] VEP amplitude (Halliday et al 1973a) Therefore the latency shift of VEP [illegible] to be established at the time of the acute optic neuritis and did not appear [illegible] influenced by the recovery processes which lead to an increase of the amplitude

In this hospital all patients with acute optic neuritis have been registered [illegible] followed for years by regular neurological and ophthalmological check-ups [illegible] brospinal fluid abnormalities and HLA types have also been determined [illegible] Wollheim 1975 Sandberg Wollheim et al 1975) Preliminary VEP recordings [illegible] some of these patients revealed an unexpectedly large proportion of patients [illegible] normal or almost normal VEP latencies In order to penetrate this [illegible] further an unselected group with varying degrees of remaining ocular [illegible] optic neuritis was tested with VEP The results were correlated [illegible] symptoms and signs frequency of remaining defects and number of cases [illegible] ing signs of multiple sclerosis

As the present study proceeded the authors had the opportunity of [illegible] group of new cases of optic neuritis with repeated VEP tests from the [illegible] phase of the disease and up to two years afterwards The purpose of this [illegible] study was firstly to confirm that patients with symptoms of acute optic [illegible] exhibit characteristic VEP abnormalities when tested and measured [illegible] techniques and secondly to follow the time course of normalization

A preliminary account of the results has been published (Rosen et al 1[illegible]

Material

The material consisted of 42 patients 18 males and 24 females who were [illegible] observation after an episode af acute unilateral optic neuritis Their ages [illegible] of the final examination ranged between 23 and 51 years (mean 3[illegible] observation time from the onset of the disease to the final check-up ra[illegible] to 8 years (mean 4 3)

At the time of the acute episode the majority of the patients suffe[illegible] retrobulbar pain and all of them had reduced vision in the affected eye T[illegible] acuity was 0 9–0 6 in 13 cases 0 5–0 2 in 12 cases and 0 1 or less in 1[illegible] patients exhibited defective colour vision and central visual field defects T[illegible] disc of the affected eye was normal (retrobulbar neuritis) in 34 patients and [illegible] (papillitis) in 8 In one single case there was amblyopia due to anisometrop[illegible] diseased eye

Methods

ts

attern stimulation was produced by an electronically controlled stimulator compris atrix of 64 light-emitting diodes (response time 90 ns stimulus frequency 1 Hz) half n were lit at a time and switched to provide pattern reversal (Evans et al 1974) Two sized screens were used One provided a matrix of dots and the other a checker board The electronic control device and hence the timing of reversal was identical for the ts of stimuli The patients were placed 1 5 m in front of the screen at which distance nination was 0 008 lux The luminance of the dots of the dot screen was 640 cd m² the screen area) The luminance of the squares of the checker board screen was 45 50% of the screen area) The visual angle for each of the screens was 3 3 and between acent dots/squares 25 The diodes of both screens emitted a yellow light. The test was ned in a light room with the patient s gaze fixed at the upper edge of the screen Our perience is in agreement with that of others in that selective stimulation of the lower eld causes minimal variability of the response (Halliday 1972 Lehmann & Mir 1976) gle channel bipolar lead (C – O) was used The signal was amplified by a regular EEG er (0.3–70 Hz) and 2 × 100 traces for each stimulus and eye were a eraged in a Didac eraging computer and photographed for documentation

latency of the dominant positive (positive at neck) deflection P100 was determined as the amplitude from this peak to the following negative peak of the response This ide was chosen because it was sometimes difficult to define a negati e peak preceding This was never the case with the negativity following P100

149 patients pattern reversal VEP tests from both eyes were made at least once i e at e of the final check up In 13 patients repeated VEP tests were performed during the ition time from the initial acute phase of the disease and up to two years afterwards In n one patient was examined with repeated VEP tests from the acute phase of the (Fig 2) As the observation time was only 4 months he was not included in the rest of dy Altogether 149 pattern reversal VEP tests were made bilaterally

Table I

lues for the normal control group (28 eyes in 14 subjects age 23 58 years (mean 33 6 years)

	P100 latency (ms)		Amplitude (µV)		Side-difference (ms)		Side-difference (µV)	
	M	SD	M	SD	M	SD	M	SD
rn reversal s	89.5	9 6	5 6	2 3	0 2	0 8	0 7	0 7
rn reversal cker board	109 5	7 0	5 9	2 3	4 0	5 5	0 7	0 6

For reference identical VEP determinations were made on ... whose age distribution was similar to that of the patients (23–59 years ...) Repeated recording of VEP gave variations of P100 latency of less than 5 ... time The constancy of the P100 latency at repeated tests is also demonstr... clinically unaffected eye in the present clinical material (Fig 2B)

Clinical eye examinations

Repeated routine ocular examinations were made in all 49 patients ... check up a detailed neuro-ophthalmological examination was performed ... cases by one of us assisted by a well trained ophthalmic technician On ... the visual acuity was tested with Monoyer s 2 0-table and the colour ... Bostrom Kugelberg s pseudo-isochromatic plates The visual fields were ... with Goldmann s kinetic perimeter Several white test objects were ... particular care was taken to map the central field and to compare the results ... eyes as regards the position and shape of the isopters Swinging flash ... and low intensity was used to test the pupillary light response ... included examination of the retinal nerve fibre layer with intense red-free light

Neurological examinations

All patients underwent a neurological examination and a lumbar puncture ... onset of ocular symptoms None of the patients had had previous ... symptoms including optic neuritis and a thorough examination was ... each case In the CSF a pleocytosis was found in 58% and in 40% two or ... bands in the gamma globulin fraction on agar gel electrophoresis were ... strated In patients with MS an oligoclonal gamma globulin pattern is the common CSF abnormality (Laterre et al 1970)

The HLA type of each patient was determined earlier (Sandberg Wadhem 1975) by serotyping for 23 different HLA antigenes and by MLC-typing ... In the present patient material 11 patients carried HLA A3 19 patients ... HLA B7 and 18 patients were DW2 positive

During the observation period each patient was re-examined at least once in order to establish whether or not the patient had developed symptoms ... of MS The last neurological examination was undertaken on the same occ... the final ophthalmological examination and the VEP-test. Altogether ... 42 patients developed signs of lesions in other parts of the CNS du... observation time and were considered to suffer from MS

Statistical methods

Student s t test was used for comparison of independent sets of measurements and ... for comparison of frequencies

The final evaluation was made blindly i e none of the examiners knew the result ... other two

Results

ference to the results of the VEP tests of the 14 normal subjects (Table I) the nts were grouped into three d fferent categones accord ng to the latencies l (Table II A) Group I consisted of 12 patients with completely normal VEP i e a normal latency time a latency prolongation of the response from the eye as compared with the unaffected eye of less than 3 ms (mean of dot and board values) Group II comprised 21 cases with a latency prolongation of from the affected eye of more than 3 ms (range 3 70 5 ms) Only 5 of the had latency differences between the eyes of less than 10 ms Group III d of 9 patients showing P100 latencies above the normal range from *both*

nitial mean visual acu ty of the affected eye was 0 55 (SD 0 39) in group I 7 (SD 0 29) in group II It had thus been significantly better in the group of with normal VEPs than in the group with abnormal VEPs ($P < 0\ 05$) The ce of other initial ocular symptoms and s gns were found to have been listributed in both groups

orrelation was found between VEP latencies and the ultimate visual acu ty er when other remaining ocular s gns were taken nto account i e defective on visual field defects reduced afferent pupillary l ght response and trophy s gnif cant differences existed between the groups Thus the with normal VEPs exhibited s gnificantly fewer remaining ocular s gns ose with abnormal VEPs ($P < 0\ 005$) Table III

Table II A

Subd s on of patients from VEP criteria

No	Criteria	Age		Observation time (years)	
		Range	Mean	Range	Mean
12	Normal VEP Latency prolongation on affected s de less than 3ms	25 4	31 9	2 8	5
21	Pathological VEP from affected eye Latency prolongat on more than 3 ms	20 50	33 4	1	3 5
9	Pathological VEP from both eyes	28 51	33 9	1 5	5 1

Table II B

VEP values for the three subgroups of patients

			P100 latency (ms)		Amplitude (μV)		Side-difference (ms)		Side-difference (μV)	
			M	SD	M	SD	M	SD	M	SD
Affected eye	Dots	I	87 8	5 2	4 4	2 4	−0 9	3 7	0 19	1 0
		II	108 0	20 6	3 8	2 0	17 9	17 0	1 20	1 2
		III	134 3	11	3 6	1 1	12 0	19 8	1 1	1 5
	Checkerboard	I	9[illegible] 5	9 3	4 7	1 9	1 0	2 8	−0 3	1 4
		II	120 9	2[illegible] 1	4 [illegible]	3 0	22 6	20 1	1 7	1 8
		III	133 8	19 3	4 4	2 2	9 7[illegible]	19 7	0 1	1 6
Healthy eye	Dots	I	8[illegible]7	[illegible] 0	4 [illegible]	[illegible] 2				
		II	[illegible]	8 4	[illegible] 0	2 [illegible]				
		III	[illegible]	[illegible]	4 7	1				
	Checkerboard	I	[illegible]	8 [illegible]	4 4	1 [illegible]				
		II	[illegible]	[illegible]	[illegible]	[illegible]				

Table III

Clinical ophthalmological findings at the time of the final check up

	Entire group	I	II	III
Reduced visual acuity	1 /39 (38%)	4/11 (36%)	9/ 0 (45%)	?/8 (25 %)
		$P > 0.05$		
Defective colour vision	11/39 (?8%)	0/11 (0 ?)	9 20 (45%)	2/8 (25%)
		$P < 0.05$		
Visual field defect	16/39 (41%)	?/11 (18%)	11/20 (?5%)	3/8 (38%)
		$P < 0.05$		
Reduced afferent pupillary light response	16/39 (41%)	2/11 (18%)	12/20 (60%)	2/8 (25%)
		$P < 0.02$		
Optic atrophy	2.5/39 (64%)	4/11 (36%)	17/20 (85%)	4/8 (50%)
		$P < 0.01$		
Σ Pathological signs	2 13 ± 1 73	1 09 ± 1 15	? 90 ± 1 59	1 63 ± 1 69
		$P < 0.005$		

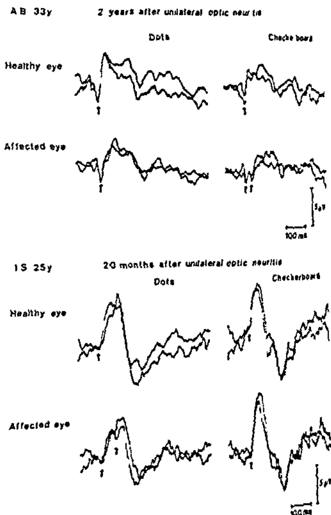


Fig 1

Pattern reversal visual evoked potentials recorded from two different patients at the *final* check up For details of stimulation and recording see Methods Voltage calibrations are given in the figure The patient A B showed a slightly defective a paracentral visual field defect and a pale optic disc in the affected eye The I showed a slight reduction of visual acuity in the affected eye but no other residual The visual acuity at the time of the acute optic neuritis was 0 9 for A B and 0 P100 latency during the initial phase was 165 ms for A B and 195 ms for I S A B showed a pleocytosis of CSF and I S a pathological agar gel-electrophoresis

"e three groups of patients did not differ in terms of frequency of initial rmal CSF findings or distribution of HLA types A3 B7 and DW2 Altogether he 42 patients developed signs of lesions in other parts of the CNS during the ation time and were considered to suffer from multiple sclerosis Three of belonged to group I i e those with normal VEPs and one case to group III hose with bilateral VEP abnormalities

r the normal controls as well as the clinical material the P100 latency was matically longer with checker board stimulation than with dot stimulation les I and IIB) The average difference calculated for each of the normal eyes 13 0 ms (SD 9 2 ms) A similar difference was seen for the eyes affected by optic itis (average difference 10 0 ms) as well as the fellow eyes (8 1 ms)

ne difference of latency between the affected and fellow eyes was about the for dot and checker board stimulation (average difference with dot stimula 11 6 ms as compared with 13 9 ms for checker board stimulation) In the up of 21 patients with pathological latency prolongation from the affected eye howed a larger latency difference with checker board stimulation and 9 a larger rence with dot stimulation In one case the latency difference was exactly the e with the two types of stimulation

s regards the shape of VEP clearcut differences were found in individual cases the two types of stimulation Examples are given in Fig 1 In case A B dot ulation produced symmetrical responses but checker board stimulation ked a bi phasic P100 response from the affected eye In case I S dot stimulation duced a somewhat lower amplitude response with a notch from the affected eye response to checker board stimulation being almost identical

For the 14 cases followed by repeated VEP tests from the initial phase of the ase and up to two years afterwards the P100 latencies for the affected and ffected eye were plotted in Fig 2A and B The course of the VEP latency shifts ied individually but the three groups of patients i e those with normalized Ps (Group I) with remaining latency asymmetry (Group II) and with bilateral ncy prolongation (Group III) could be identified Group II was further divided into Group IIA with entirely unaffected VEP latency on the clinically affected eye and Group IIB with an initial slight latency prolongation also for the ically unaffected eye A similar initial latency prolongation on the unaffected eye s seen for one patient in Group I (Fig 2B) For the affected eye a rapid as well as more prolonged phase of recovery of latency over several months could be tinguished In most cases the amplitude underwent a faster recovery than did the ency usually reaching a peak after 2–4 months Then there was a general ndency of the amplitudes to return to a somewhat lower level than for the nically healthy eye

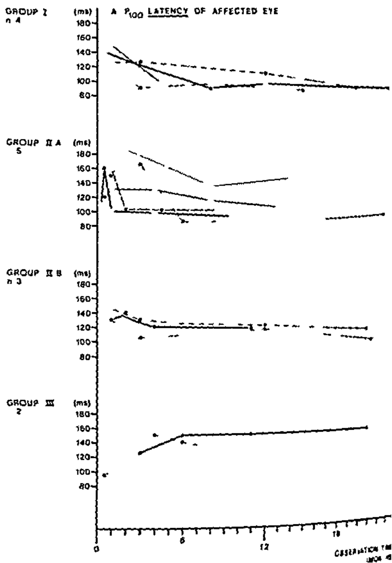

A P_{100} LATENCY OF AFFECTED EYE
GROUP I
n 4
GROUP II A
5
GROUP II B
n 3
GROUP III
2
(ms)
180
160
140
120
100
80
0
6
12
18

Fig 2 A

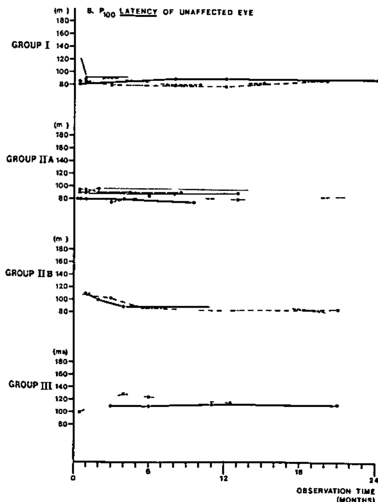


Fig 2 B

Fig 2 A and B

ngitudinal follow up of 14 cases of acute optic neuritis A P100 latency of affected eye B
00 latency of unaffected eye Groups I II and III patients fulfilling the criteria of VEP
ponses at the time of final check up according to the classification given in Table IIA
oup IIA patients with remaining VEP asymmetry and with no significant change of
ncy from the fellow eye Group IIB patients with remaining latency asymmetry and with
an initial latency prolongation also from the clinically unaffected eye

Discussion

Twelve of our 42 patients (29%) with a previous episode of acute optic [illegible] a normal pattern reversal VEP This frequency is much higher than in the [illegible] of Halliday et al (1972 1973a) and Shahrokhi et al (1978)

Our stimulating technique differed from that used by these authors [illegible] lower luminosity (45 cd/m² as compared with 110 cd m² for the [illegible] squares) and a smaller screen (3 3 as compared with 8 [illegible]). However [illegible] cannot explain the high number of normalized VEP latencies in our [illegible] According to Nilsson (1978) a low intensity pattern reversal stimulus [illegible] emitting diodes from a 3 9 screen turned out to be more sensitive in [illegible] abnormal responses than a high intensity checker board stimulus from a [illegible] screen (1000 cd/m² 8 8) The method of selective stimulation of the lower [illegible] the visual field does not seem to decrease the proportion of abnormal [illegible] patients with multiple sclerosis (Lehmann & Mir 1976) Furthermore [illegible] influencing the absolute values of amplitudes and P100 latencies the method [illegible] stimulating recording and measuring the VEP responses can hardly [illegible] relative changes on the affected eye at repeated examinations of the [illegible] individual

One explanation of the results obtained may be that our material [illegible] greater number of cases with mild optic neuritis The observation that the [illegible] visual acuity of the affected eye was significantly better and the fact that there [illegible] fewer remaining ocular defects in the group with normal VEPs than in the [illegible] with abnormal VEPs give some support to this hypothesis

Another explanation of the divergent results may be that in previous [illegible] the optic neuritis was often a sign of generalized MS It is not known to what [illegible] the remaining latency prolongation of VEP is a sign of disseminated [illegible] or a remnant of the acute episode of optic neuritis Patients with the [illegible] MS often develop bilateral latency prolongation of VEP without any history of [illegible] neuritis (Bynke et al 1977) Only a small proportion of patients with acute [illegible] neuritis develop signs of generalized MS (Sandberg Wollheim 1979 B[illegible] 1979)

The incidence of other initial ocular symptoms and signs and of CSF abnor[illegible] lities was evenly distributed among the patients making it very unlikely [illegible] patients with normal VEPs had another type of disease than those [illegible] abnormalities

Furthermore the longitudinal study with repeated VEPs during the [illegible] phase supports the assumption that the initial disease was an organic [illegible] the optic nerve

In agreement with the results of Halliday et al (1973a) no correlation was [illegible]

een the VEP latency prolongation and the final visual acuity However a lation was found between the VEP latency and other remaining ocular signs A sophisticated test battery including more detailed examinations of the central al field more subtle tests for colour vision and differences between eyes of eption latency (Rushton 1975 Galvin et al 1976 Slagsvold 1978) would umably have demonstrated even more clearcut correlations between VEP icy and clinical findings after optic neuritis

he study shows that a normal and symmetrical pattern reversal VEP test months ears after an acute episode of unilateral eye symptoms does not in any way ude the possibility that this episode was due to optic neuritis

he VEP values after acute optic neuritis from our experience do not give lictive information as to the risk of developing multiple sclerosis Three of four s of multiple sclerosis occurred among the patients who had normal VEP ncies after the episode of the optic neuritis

e found a bilateral VEP latency prolongation after unilateral optic neuritis in cases (Group III) Amblyopia is known to produce not only amplitude changes also latency prolongation either from the amblyopic eye or from the fellow eye inger & Nilsson 1978) In only one of the nine cases the diseased eye was also olyopic In the other eight cases a reasonable explanation of the VEP latency longation from the fellow eye is a subclinical optic neuritis of that eye In one of m was the latency prolongation of the contralateral eye observed to develop ing the follow up period Moreover among the 14 cases followed during the phase at least four showed an initial latency prolongation from the fellow eye nonstrating that this eye was not entirely unaffected (Fig 2)

There was a systematic difference of latency between dot and checker board nulation in the present study both among normal subjects and among patients h optic neuritis despite identical timing of the stimulus and identical size of the een The response amplitude produced by the two types of stimuli was similar erage value of 5 6 μV for dot stimulation as compared with 5 9 μV for ecker board among normal controls) The two types of stimuli differ in form and minosity (dots circles 3 mm diam 640 cd/m² checker board squares 1 cm² 45 /m²) The earlier latencies for dot stimuli cannot be attributed to the difference of minosity only because Nilsson (1978) found shorter latencies for dot stimulation an for checker board stimulation of considerably higher luminosity The pos ility may be considered that partly different groups of nerve fibres or cortical eurones were involved in the two types of test The investigation does not indicate at any of the two types of stimulation is especially sensitive in revealing remaining nduction abnormalities after demyelination In practice we have found it of value apply both types of stimuli when using VEP as tests of disseminated CNS myelination

Acknowledgments

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References

Asselman P Chadwick D W & Marsden C D (1975) Visual evoked responses in the diagnosis and management of patients of multiple sclerosis Brain 98 61 ...

Brit Med J (1979) Leading Article Prognosis of optic neuritis 1 775

Bynke H Olsson J E & Rosen I (1977) Diagnostic value of visual evoked response, clinical eye examination and CSF analysis in chronic myelopathy Acta Neurol Scand 56 55 ...

Evans B T Binnie C D & Lloyd D S L (1974) A simple visual pattern stimulator Electroenceph clin Neurophysiol 37 403–406

Galvin R J Regan D & Heron J R (1976) Impaired temporal resolution of vision after acute retrobulbar neuritis Brain 99 255–268

Halliday A M (1972) Discussion on component analysis and topology In Specific evoked potentials Trace 6 39–46

Halliday A M McDonald W I & Mushin J (1972) Delayed visual evoked response in optic neuritis Lancet I 982–985

Halliday A M McDonald W I & Mushin J (1973a) Delayed pattern evoked responses in optic neuritis in relation to visual acuity Trans ophthal Soc UK 93 315–3..

Halliday A M McDonald W I & Mushin J (1973b) Visual evoked response in diagnosis of multiple sclerosis Brit Med J 4 661–664

Laterre E C Callewaert A Heremans J F & Sfaello Z (1970) Electrophoretic analysis of gammaglobulins in cerebrospinal fluid of multiple sclerosis and other diseases of the nervous system Neurology (Minneap) 20 982–990

Lehmann D & Mir Z (1976) Methodik und Auswertung visuell evozierter EEG-P... bei Verdacht auf multiple Sklerose J Neurol 213 97–103

Matthews W B Small D G Small M & Pountney E (1977) Pattern reversal evoked potential in the diagnosis of multiple sclerosis J Neurol Neurosurg Psychiat ... 1009–1014

Nilsson B Y (1978) Visual evoked response in multiple sclerosis comparison of ... for pattern reversal J Neurol Neurosurg Psychiat 41 499–504

Rosen I Bynke H & Sandberg M (1979) Pattern reversal visual evoked potentials in unilateral optic neuritis Proceedings of the International Evoked Potentials Symposium Nottingham 1978

Rushton D (1975) Use of the Pulfrich pendulum for detecting abnormal delay in the visual pathway in the multiple sclerosis Brain 98 283–296

berg Wollheim M (1975) Optic neuritis studies on the cerebrospinal fluid in relation to ical course in 61 patients Acta neurol. Scand. 52 167 178

berg Wollheim M (1979) Optic neuritis cerebrospinal fluid findings and clinical course cerpta Medica, Proceedings XXIII International Congress of Ophthalmology Mav ,8

berg Wollheim M Platz P Ryder L. P Staub Nielsen L. & Thomsen M (1975) HLA tocompatibility antigens in optic neuritis Acta neu ol. Scand. 52 161 166

rokhi F Chiappa K. H & Young R. R. (1978) Pattern shift visual evoked responses o hundred patients with optic neuritis and or multiple sclerosis. Arch Neurol. 35 64 71

rold J E. (1978) Pulfrich pendulum phenomenon in patients with a history of acute ic neuritis Acta ophthal. (Kbh.) 56 817–826

ger P & Nilsson B Y (1978) Visual evoked responses to pattern reversal stimulation in tients with amblyopia and or defective binocular functions Acta ophthal. (Kbh.) 56 ,–697

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APPLICATION OF TWIN FLASH STIMULI FOR SOME MACULAR DISEASES
ISOLATION OF LOCAL RESPONSES BY TWIN FLASHES

BY

MARIKO MITSUYU YOSHIHITO HONDA and AKIRA NEGI

Double flash ERG was examined for patients with visual loss from macular and optic nerve disorders and the responses were compared. K values ((B - B2)/B1 × 100) of the former were larger than normal values when the stimulus intervals were between 200 and 500 mseconds and abnormality of K values seemed to correspond to the functional impairment of macula. On the other hand K values of the patients with optic nerve diseases remained in the normal range These facts indicate that double flash ERG is a very useful method to estimate the cone function clinically and can be employed as a routine examination for patients with suspected cone dysfunction

Key words double flash (twin flash) – stimulus intensity – stimulus interval – K (= (B1 B2))/B1 × 100) – macular degeneration

In our previous works double flash ERG was studied on rod-dominated, cone-dominated and mixed retinas of mammals and its usefulness in separating the cone function was emphasized (Mitsuyu 1978a b) This time the double technique was applied to patients with visual loss from macular and optic disorders and difference of responses was investigated

Materials and Methods

Nine normal volunteers (aged between 25 35) and seven patients were examined. The tested eye was previously fully mydriated with phenylephrine hcl (0 5%) and tropicamide (0 5%) drops Benoxinate was dropped on the cornea a corneal contact lens electrode of Kawabata's type was attached as an

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le Reference electrode was attached on the earlobe The electric signal was ·d by pre amplifier (time constant 0 3 seconds) and photographed Diffuse ght was delivered by a xenon flashtube which was designed to discharge a (twin) flash of the same energy in the range from 0 3 joule to 2 0 joule The between the first and second flash within a pair could be freely changed In estigation the interval remained between 50 mseconds and 1000 mseconds ~0 min in the dark double flash stimuli were applied continuously When des of ERGs became constant stimulus intervals of the double flash were d from 50 mseconds to 1000 mseconds and the responses were compared mulus frequency of the double flash was always 0 1 Hz and stimuli of several zes were employed The amplitudes of the ERGs by the first and the second were measured from the bottom of the a wave to the top of the b-wave as ed in Fig 1 and were named B_1 and B_2 The index $(B_1 B_2)/B_1 \times 100$ (named calculated for every pairs

Results

ponses from normal controls

ılt of normal controls is shown in Fig 2 In this experiment, stimulus ties of 0 3 0 6 and 2 0 joule were used Fig 3 shows the Ks obtained from l controls when the stimuli of 0 3 joule were used Responses from nine luals were averaged When the stimulus interval was shorter than 100 nds the second ERG barely appeared and K was 100 When the stimulus l became longer than 100 mseconds the ERG appeared With prolongation inter stimulus intervals the B_2 increased and accordingly K decreased At terval of 400 mseconds an inflexion is observed in the curve Then the l ERG increased rapidly with an increase in the inter stimulus intervals and ·d almost the same amplitude of B_1 at 700 mseconds

ig 4 Ks of 2 0 joule stimuli are shown In this case a measurable ERG was ied by the second flash when the stimulus intervals was as short as 100 nds, on the discending shoulder of the first b-wave When the stimulus



Fig 1
B and B_2 were measured as indicated in this figure

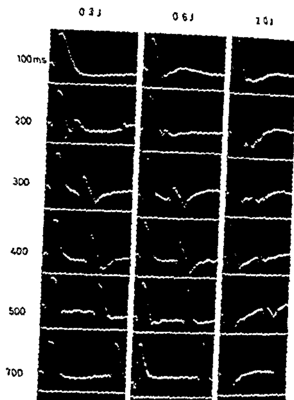


Fig 2
Double flash ERG of a normal control Stimulus intensities of 0.3 ... joule were employed Stimulus intervals were between 100 msec ... Calibration 50 microvolt.

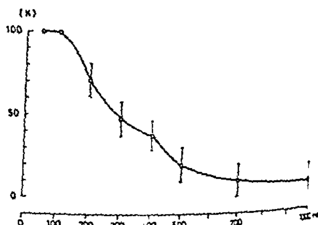


Fig 3
K values (= (B1 B2) B1 × 100) of normal controls when the stimulus ... Numbers along the ordinate represent K values and those along the ... interval Nine experimental values were averaged and are shown ...

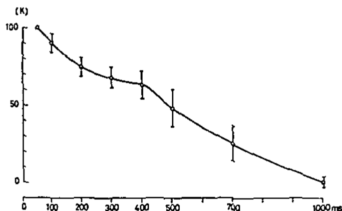


Fig 4

l controls when the stimulus intensity was 2 0 joule Nine experimental values were averaged

was shorter than 400 mseconds B2 amplitude did not increase as rapidly as intensity of 0 3 joule Accordingly K of 2 0 joule decreased slowly and a f inflexion was made at 400 mseconds K decreased more rapidly for the us intervals

plication of double flash ERG for patients with macular diseases

atients were examined One of the results (case 5) is shown in Fig 5 K values ied from these five patients are indicated in Table I

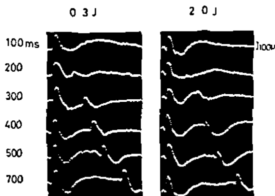


Fig 5

Double flash ERG of the case 5 right eye

Table I

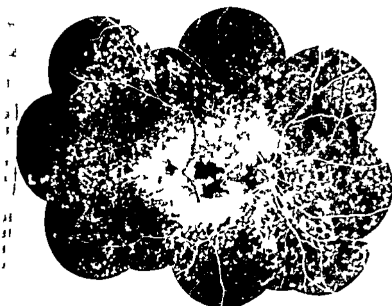
K values of normal controls and those of case 1 5 For the case 1 5 all ... indicated Normal values are given by averaging of nine experiments ...

Intensity	Interval mseconds	Normal SD	Case 1 R	Case 1 L	Case 2 R	Case 2 L	Case 3 R	Case 3 L	Case 4 R	Case 4 L	
0 6 J	100	100 (0)	100	100	100	90	100	100			[illegible]
	200	71 (10)	71	77	90	71	55	5	[illegible]	73	[illegible]
	300	48 (10)	59	82	70	50	57	56	60	[illegible]	[illegible]
	400	38 (9)			56	50	46	40	60	[illegible]	[illegible]
	500	20 (11)	25	57	61	36	[illegible]	[illegible]			[illegible]
	700	10 (10)	0	20			0	[illegible]			
2 0 J	100	90 (6)	95	100	100	95	100	55			
	200	75 (6)	94	85	100	83	9	83			[illegible]
	300	67 (7)	82	89	90	[illegible]	[illegible]	88			[illegible]
	400	63 (9)			18	6	5	[illegible]			[illegible]
	500	48 (12)	56	64	67	61	69	60			[illegible]
	700	[illegible] (12)	14	24			44	[illegible]			

(Case 1) Thirty year-old male His visual acuity was 0 1 (n c) for the right eye and ... for the left eye By Ishihara & Farnworth Panel D-15 hue test, he was diagnosed ... totally colour blind His macula was degenerated and a snail-slime reflex ... surrounding area of the macula was grayish clouded and black bone-corpuscle ... were seen in the retina When the fundus was very carefully examined, ... spots were seen in this area Fluorescein fundus angiography (Fig 6) revealed ... indicating fundus flavimaculatus His single flash scotopic ERG was ... But as it shown in Table I most values of Ks in the double flash ERG of the ... the stimulus intervals of 200 mseconds and 500 mseconds were larger than normal ...

(Case 2) Twenty year-old male came to the Kyoto University Hospital ... progressing visual loss His visual acuity was 0 01 (n c) for the right eye and ... eye Colour vision was tested by Ishihara & Farnworth Panel D-15 and ... totally colour blind his left eye being normal By funduscopy ... was seen for the right eye and a slight change was also seen for the left eye ... was flat for both eyes showing widespread pigment epithelial dysfunction ... were above the normal range for both 0 8 joule and 2 0 joule stimulus intensities ...

(Case 3) Twenty three year-old male was an elder brother of the case 2 He ... complaint but his left fundus showed a definite macular change very ... brother s left eye and visual acuity was slightly decreased (0 8 n c) Right eye ... normal Electrooculogram did not show light rise and pigment epithelial ... to exist Ks were within normal range for the stimulus intensity of 0 3 joule ... stimulus intensity was 2 0 joule Ks were above normal at the stimulus ... mseconds and 300 mseconds for the left eye and at 500 mseconds for the right eye ...



F g 6
Fluoresce n fundus angiography of the case 1 (right e e)

) N neteen year-old female had severe visual loss for several yea s She compla ne l of hobia and could not see well under bright l ght Her sual acu ty was 0 1 (n c) for yes She was totally colour blind by Ish hara & Farnw rth Panel D 15 l ue test Her was nearly normal on ophthalmoscopy and fluoresce n fundus angi graphy ex ept central reflex was seen She was diagnosed as progress e cone dysfunctı n syn l me as type She was examined using double flash ERC f 0 3 y ule s mulus n ens ty Ks ons dered to be abo e the normal range

5) Twenty four year-old female complained f v sual loss n l e r gl t eye wh cl l a l several months before Her isual acu ty was 0 l n c) f r tl e r gl t eye and l f r tl e e. Funduscopy revealed a severe degenerative change w tl l lack p g ner ts at l er r gl t a. A sl ght change was also seen in the macula area f the left eye F g shows tl e e flash ERG of the right eye of th s patient Ks were ll n rmal wl en s ulus te s y joule was examined ks were ab e normal between the st l s ervals f 100 onds and 400 mseconds

oub e flash ERG n the patients w th visual lo s caused by opt c nerve d sorde s

patients were examined

6) Th rty-three year-old male complained d v s al loss n tl e r gl t eye for a month, n the left eye for several years His visual acu ty w s 0 2 (n c) f r the right eve, and (n.c) for the left eve On ophthalmoscopy the disc l w f tl e r ght eye was almost

Table II
K values of case 6 and 7

Intensity mseconds	(Case 6) 0.33 R	(Case 6) 0.33 L	(Case 7) 0.33 R	(Case 7) 0.33 L	(Case 7) 0.? R	(Case 7) 0.? L
100	100	100	100	100	[illegible]	[illegible]
200	[illegible]	63	[illegible]	[illegible]	[illegible]	[illegible]
300	[illegible]	41	[illegible]	[illegible]	[illegible]	[illegible]
400	[illegible]	[illegible]	36	[illegible]	[illegible]	[illegible]
500	13	[illegible]	7	[illegible]	[illegible]	[illegible]
700	0	0	14	7	1	[illegible]

normal but that of the left *eye was a little pale at the temporal margin.* Table [illegible] values of this patient. All values are within or slightly below the normal range [illegible] found to be *suffering from multiple* sclerosis.

(Case 7) Forty year-old male had *optic nerve atrophy* and his visual acuity was [illegible] both eyes. As is shown in Table II Ks were *within or slightly below the normal range.*

Discussion

Double flash ERG has been *examined for* human subjects by some [illegible] (Burian & Spivey 1959 Elenius 1968 Algvere & Westbeck 19[illegible] [illegible] Rouck (1962) and Elenius (1969) studied it on patients with cone dysfunction [illegible]

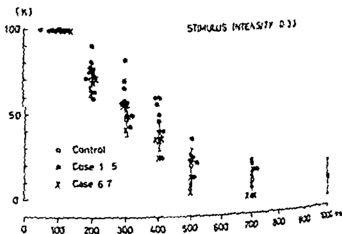


Fig 7
K values *of the case 1 7 are plotted with* [illegible] ntrol values. Stimulus intensity [illegible]

ter showed that in two totally colour blind patients the second ERG ared in a test condition Although some investigators tried to use the double chnique clinically (Sverak et al 1962) routine employment of it has not been ported In this study double flash technique was applied to patients with disturbance from macular and optic nerve disorders The former showed ntly abnormal value of K whereas the latter showed a normal value In Figs 3 the differences of K values are clearly shown between these two groups It that double flash ERG is a useful tool in the differential diagnosis of visual ance from macular and optic nerve diseases As shown in case 2 and 3 nality of K might correspond to the functional impairment of macula and K between the stimulus intervals of 200 mseconds and 500 mseconds seemed to portant Double flash ERG is very convenient way to measure the cone on quantitatively though at present information about it is not enough Other tages of double flash ERG are that it is easy to perform clinically and not onsuming Because the recorded ERGs are considerably large the measure of ERG amplitudes are always easy and accurate without employing ing technique It is concluded that the double flash ERG is a very useful ophysiological method to separate cone and rod function and that it can be oyed as a routine examination for patients with suspected cone dysfunction

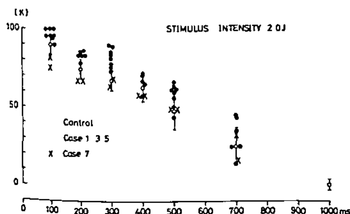


Fig 8

Values of the case 1 3 5 and 7 plotted with control values Stimulus intensity was 2 0 joule

References

Algvere P & Westbeck S (1972) Human ERG in response to double flash during course of dark adaptation A Fourier analysis of the oscillatory potentials [illegible] 195–214

Burian H M & Spivey B E. (1959) The effect of twin flashes and of repeated [illegible] the human electroretinogram Amer J Ophthal. 48 [illegible]

Elenius V (1968) Double flash ERG in central serous retinopathy [illegible] 976–979

Elenius V (1969) Cone and rod activity in the electroretinogram [illegible] light. Arch. Ophthal. (Chicago) 81 618–621

Francois J & De Rouck A (1962) The use of twin flashes in electroretinographic [illegible] ties of the electroretinogram in normal cases and in chorioidoretinal [illegible] Amer J Ophthal 54 54–63

Mitsuyu M (1978a) The double flash ERG during adaptation to the dark [illegible] 56 291–301

Mitsuyu M (1978b) Studies on the double flash ERG of pigeons [illegible] 877–882

Sverak J Wassermannova V & Peregrin J (1962) Electroretinographic [illegible] problems of the pathogenesis of central serous retinopathy [illegible]

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VISUAL EVOKED RESPONSES TO PATTERN REVERSAL STIMULATION IN CHILDHOOD AMBLYOPIA

BY

PETER WANGER and HANS E PERSSON

V sual evoked responses to monocular and b nocular pat ern re ersal stimula tion were recorded in ten normal and twentythree amblyop c ch ldren In twenty of the twenty three ch ldren wi h amblyop a the responses were found to d ffer from those n the normal group n one or se eral of the follow ng parameters s de d fference of ampl ude s de d fference of latency ampl tude in rease to binocular stimulat on The described me hod can be of alue as an aid n d agnosis of amblyop a

Key words sual e oked responses pattern re ersal stimulation monocular and b nocular stimulation amblyop a ch ldhood

ctional amblyopia is cons dered to be curable f diagnos s s made and treatment ted at an early age (Bishop 1975) An objective techn que for diagnos s would iously be of value as the results from psycho-phys cal examination of young ldren are not always rel able

The record ng of visual evoked responses (VER) offers a possibility of objective amination of the visual system Judging from several studies (e g Spekre jse et al 72 Arden et al 1974 Sokol & Shaterian 1976 Levi & Harwerth 1978 Srebro 8 Wanger & Nilsson 1978) amblyopia can be demonstrated by VER exam na n pro ided that the stimulus is adequately chosen i e consisting of a revers ng ckerboard pattern (Spekreijse et al 1972 Arden et al 1974 Levi & Harwerth 8) with small checks (Sokol & Shaterian 1976) poss bly also low contrast tween squares (Spekreijse et al 1972 Barnard 1978) and low reversal frequency ebro 1978 Wanger & N lsson 1978)

ce ed February 1 1980

In the present study these aspects of the stimulus parameters [illegible] into consideration and the results from examination of 23 child[illegible] and 10 normal children are reported

Material

The normal group consisted of 10 healthy children age 4-6 years, [illegible] visual acuity and without history of squint or subnormal vision among [illegible] siblings

The pathological group consisted of 23 children age 4-6 years [illegible] referred to ophthalmological examination because of subnormal [illegible] found at the general health examination which is performed on all children [illegible] of age in Sweden at the Children Health Care Centers. All cases in the gr[illegible] examined by an experienced ophthalmologist who made a general [illegible]cal examination including retinoscopy with atropine mydriasis. Refra[illegible] were corrected and the prescribed glasses were also used during the [illegible] recordings

Methods

Stimulation

Pattern reversal stimulation was obtained with a commercially a[illegible] TV pattern [illegible] (Medelec) A checkerboard pattern was presented on a standard [illegible]-inch TV set [illegible] the patient at a distance of 1 5 m The whole stimulating field corresponded to a [illegible] of 15 2 and each square subtended a visual angle of 1°' The average luminance [illegible] screen was 45 cd/m² with a contrast between squares of 50% Monocular [illegible] eye and binocular (dioptic) stimulation was used with a pattern reversal frequen[illegible]

Recording

The VER was recorded between an electrode applied to the scalp 5 cm above the [illegible] midline (0z) and a midfrontal reference (Fz) The signals were fed into a [illegible] low and high frequency filters set at 0 8 and 80 Hz, respectively Responses to 1[illegible] reversals were averaged on a Medelec DAV 6 Analysis time was 500 ms Latency [illegible] response was defined as the time from the pattern reversal to the point of [illegible] of the early component The amplitude was measured from the preceding [illegible] the through of the early positive wave

The statistical significances were assessed by Student's t-test unless otherwise [illegible] P value of < 0 05 was considered significant

Results

al Group

esentative VERs from a normal child are shown in Fig 1 The VERs had il waveform with similar latency and amplitude to stimulation of each eye and ed amplitude increase to binocular stimulation Table I presents the values of 'ER parameters in the normal group Due to the interindividual variation in itude the analysis is based on the comparison of amplitude to stimulation of resp left eye and to monocular versus binocular stimulus presentation in the individual Latency and waveform are fairly constant between individuals rett et al 1976)

ie VERs in the normal group were found to fullfill the following criteria

ide difference of amplitude less than 30% (mean + 2 SD) of the largest response onocular stimulation

ide difference of latency less than 5 ms

ncrease of amplitude to binocular stimulation more than 25% (mean − 2 SD) of argest monocular response

six of the ten normal subjects a late positive component (Parker & Salzen 1977) latency 250 ms was recorded When present this component was symmetrical to stimulation of eye but sometimes disappeared with binocular stimulation

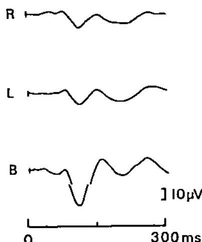


Fig 1
R from a normal individual (subject No 5) Note symmetry of amplitude and latency and amplitude increase to binocular stimulation

Table I
VER parameters in the normal group.

		VER amplitude (μV)			VER latency (ms)			[illegible]	
Subject No	Age (years)	O D	O S	Binoc.	O D	O S.	Binoc	Side diff. (%)	[illegible]
1	6	8	8	14	112	116	[illegible]	0	–
2	4	10	9	17	110	109	111	10	[illegible]
3	4	6	5	11	110	106	109	[illegible]	[illegible]
4	4	40	36	61	112	113	114	10	
5	4	15	13	32	109	108	109	13	[illegible]
6	4	10	13	21	107	[illegible]	105	3	
7	4	13	13	23	106	106	110	0	–
8	4	13	10	30	112	110	114	23	[illegible]
9	5	12	10	17	111	110	109	1	[illegible]
10	5	16	16	29	113	114	114	0	

Pathological group

The patients were ranked according to the side difference of visual acuity [illegible] in minimum angle of resolution (MAR) which corresponds to the inverted [illegible] visual acuity measured on the Snellen chart (see Table II) Based on this [illegible] pathological group was divided into two subgroups PI and PII The [illegible] subgroup PI had side differences of MAR less than 1 7 and the [illegible] subgroup PII had side differences of more than 3 2 The difference [illegible] subgroups was significant (see Methods)

Positive cover test indicating squint occurred in 36% (4/11) of the PI [illegible] and in 92% (11/12) of the PII subgroup The difference between the [illegible] occurrence of squint was also significant ($P < 0.05$ X^2–test with Yates [illegible]

Representative VERs from an amblyopic patient are shown in Fig [illegible] amplitude of the early VER component to stimulation of the right eye was [illegible] than corresponding component of the left eye The amplitude of this [illegible] was not significantly increased with binocular stimulation.

The VERs of the pathological group (see Table II) were analyzed with respect [illegible] the above mentioned criteria and the mean values and so in each group are [illegible] Table III

There was only one significant difference between the normals and the [illegible] cal subgroup PI i e binocular amplitude which was lower in the PI group

The PII group differed from the normals in all three analyzed criteria [illegible]

Case No	Age years	O D	O S	MAR	test	O D	O S	Binoc	O D	O S	Binoc	Scale diff %	Binoc / Monoc (%)
Subgroup I I													
1	4	0 4	0 4	0	±0	13	12	14	126	127	122	8	108
2	4	0 7	1 0	0 4	±0	4	4	6	134	133	135	0	150
3	5	0 7	1 0	0 4	±0	15	18	20	132	130	125	17	111
4	4	0 4	0 5	0 [illegible]	±0	8	[illegible]	6	128	121	120	37	75
5	4	0 5	0 7	0 [illegible]	+3	3	10	19	107	108	108	70	190
6	4	0 7	0 5	0 [illegible]	±0	1[illegible]	13	10	115	118	113	13	67
7	5	0 5	0 8	0 8	+10	30	[illegible]	33	123	124	125	3	110
8	5	0 8	0 [illegible]	0 8	+[illegible]	10	9	23	111	103	108	10	230
9	4	1 0	0 [illegible]	1 0	±0	13	12	17	115	116	111	8	131
10	5	0 7	0 4	1 1	±0	9	8	17	124	118	12[illegible]	11	189
11	[illegible]	0 3	0 6	1 6	+10	3	7	8	104	107	109	7	114
Subgroup I II													
12	4	0 6	0 [illegible]	3 3	+10	9	5	9	113	116	11[illegible]	11	100
13	6	0 6	0 [illegible]	3 3	+12	11	–	1[illegible]	151	–	118	100	100
14	4	0 2	0 8	3 8	+10	11	11	13	120	119	114	0	118
15	4	0 7	0 1	8 6	+10	[illegible]	[illegible]	4	10[illegible]	107	102	60	80
16	5	0 7	0 1	8 6	+3	12	4	17	128	139	117	7[illegible]	14[illegible]
17	4	0 7	0 1	8 [illegible]	+10	19	11	2[illegible]	116	156	134	1[illegible]	13[illegible]
18	[illegible]	0 [illegible]	0 1	8 9	+[illegible]	10	14	14	143	110	145	2[illegible]	100
19	5	0 1	0 9	8 9	+10	12	16	[illegible]	110	110	117	25	156
20	[illegible]	0 1	1 0	9 0	+3	4	21	21	116	10[illegible]	104	81	100
21	[illegible]	1 0	0 1	9 0	+12	12	–	11	12[illegible]	–	124	100	92
22	[illegible]	1 0	0 1	9 0	+0	7	6	0	10[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

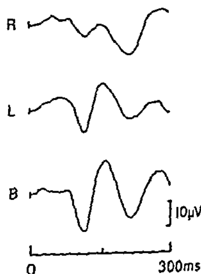


Fig 2
VER from an amblyopic patient (case No 25) Note marked side asymmetry of ... the early component and low amplitude increase to binocular stimulation

side difference of amplitude and latency and lower amplitude increase to ... stimulation

When the PI and PII groups were compared significant differences ... observed in side difference of amplitude and latency No clear correlation ... found between the degree of side difference in MAR and the magnitude ... difference of VER amplitude when these parameters were compared in ... cases

In both pathological subgroups a significant prolongation of latency ... ms) was found when the responses to stimulation of the better eye were ...

Table III
Mean and SD of analyzed VER parameters of the normals (N) and the pathological ... I II subgroups.

	N	PI	P...
Number of persons	10	11	[illegible]
Side difference of amplitude	11 ± 9%	21 ± [illegible]	11
Side difference of latency	± 1 ms	3 ± [illegible] ms	11
Binocular amplitude increase	[illegible] ± 2 [illegible]	31 ± 31 [illegible]	

corresponding responses in the normal group No such difference was ned regarding amplitudes

10 of the 23 pathological cases (43%) a late positive component was recorded stimulation of either the better or the amblyopic eye or both The late ponent usually remained with binocular stimulation

Discussion

ral investigators have studied the VER in amblyopia (for review see Srebro 3) The changes connected with amblyopia are most easily demonstrated if the ulus is a reversing checkerboard pattern (Spekreijse et al 1972 Arden et al 1 Levi & Harwerth 1978) containing small squares (Sokol & Shaterian 1976 iger & Persson 1979) Reversal frequency should not be too high (Srebro 1978 iger & Nilsson 1978) Low contrast between squares may increase the sensitivity le method (Spekreijse et al 1972 Barnard 1978)

our experience based on recording of transient responses the use of very ll checks (6') or contrast rates below 20% increases the interindividual variability makes the evaluation of the responses much more complicated (Wanger & son 1979) For this reason we have chosen a checksize of 12 and a contrast rate 0% The 2 Hz reversal frequency allows separation of the early and the late ponent (Parker & Salzen 1977)

th the described method abnormal VER was obtained in 87% (20/23) of the dren with clinically diagnosed amblyopia The three children with normal VER s 8 9 19) were found to have hyperopic astigmatic refractive errors and wed rapid normalization of visual acuity after glass correction and occlusion tment. These children presumably had a purely accommodative strabismus out established sensory adaptation

n the PI subgroup with low degree of amblyopia (VA = 0 3 or better) the only ificant VER abnormality was reduced amplitude increase to binocular stimula Two of the 11 patients in this group had abnormal side difference of latency three had abnormal side difference of amplitude In the PII subgroup with ger degree of amblyopia (VA – 0 2 or less) the VER differed from the normal up in all three criteria i e side difference of amplitude and latency respectively d amplitude increase to binocular stimulation Moreover all patients with visual ity of 0.3 or less in the amblyopic eye (Nos 11 23) except one (No 19) i e 92% d abnormal VER. Arden et al (1974) also found VER changes in amblyopia en visual acuity was below 0 3 (6/18)

It has been proposed that amblyopia is caused by suppression of the image from afflicted eye established during binocular fixation and maintained during

monocular fixation (Franceschetti & Burian 1971) The present [illegible] amplitude increase to binocular stimulation could be regarded as [illegible] suppression during binocular fixation Low amplitude and or latency [illegible] to monocular stimulation of the amblyopic eye might reflect [illegible] hypothetical suppressive mechanism also during monocular fixation The [illegible] functional disturbance causing this suppression and resulting in the [illegible] changes of the VER may be located anywhere in the visual system [illegible] retina to the site of VER generators in the cortex or at a cortical [illegible] generators Functional changes in retinal neurons (Ikeda 1979) and [illegible] (Hubel & Wiesel 1963 Guillery 1973 von Noorden 1973) and physiological [illegible] & Wiesel 1963 Ikeda & Wright 1976) changes in the lateral geniculate [illegible] (LGN) have been described in animals with experimentally induced [illegible] Since evidence has also been published for the existence of a cortico[illegible] projection to the LGN influencing the threshold of relay cells (Schmielau [illegible] 1977) a primary cortical disturbance of function may be operative Wherever [illegible] primary disturbance is located the present results with reduction of VER [illegible] to monocular stimulation of the amblyopic eye indicates an involvement [illegible] visual system peripheral to the VER generators in the cortex.

Parker & Salzen (1977) suggested that the late component of the transient [illegible] to pattern stimulation might reflect activation of the slower sustained [illegible] the visual pathway (Tolhurst 1975) Ikeda & Wright (1974) argued that [illegible] amblyopia might be due to selective lesion of this neuronal population If [illegible] assumptions are correct one would expect absence of the late component [illegible] stimulation of the amblyopic eye However absence of the late component [illegible] noted with stimulation of the better eye and presence with stimulation of [illegible] amblyopic eye in the same patient and vice versa No definite conclusion [illegible] significance of the late component can be made in the present study

It is known that defocusing of a stimulating pattern results in a gradual [illegible] in the VER amplitude (for references see Desmedt 1977) Halliday et al [illegible] found a clear relationship between the visual acuity and the mean amplitude [illegible] VER in patients recovering from optic neuritis A similar observation was [illegible] Persson & Sachs (1979) on multiple sclerosis patients with visual acuity [illegible] provoked by physical exercise (Uhthoff's symptom) In the present [illegible] correlation was found between the degree of side difference in [illegible] magnitude of side difference of VER amplitudes when these parameters [illegible] compared in individual cases It cannot be excluded that this lack of correlation [illegible] due to factors such as the limited number of patients on each visual acuity [illegible] insecurity in visual acuity testing and greater variability of attention [illegible] VER-examination of children However a clear correlation between [illegible] and VER amplitude may not be present in amblyopia since this condition [illegible]

ılt of several types of disturbances on different levels in the visual system as d above

ninary results from re examination of patients in the PII subgroup after n treatment indicated that the latency prolongation noted in some of these persistent while side difference of amplitude and amplitude increase to ar stimulation was normalized in some patients If these changes in the VER ated to clinical development the method may be useful not only as an aid osis but also for the prediction of treatment results in individual cases

Acknowledgements

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References

; B Barnard W M & Mushin A S (1974) Visually evoked responses in amblyopia *Ophthal. 58* 183–192

W M (1978) personal communication

G Blumhardt L Halliday A M Halliday E & Kriss A (1976) A paradox in the isation of the visual evoked response *Nature 261* 253–255

P O (1975) Binocular Vision In Moses R. A (Ed) Adler s Physiology of the Eye 8–648 C V Mosby Comp St Louis

l J E (Ed) (1977) *Visual Evoked Potentials in Man New Developments* Claredon Press d

chetti A. T & Burian H M (1971) Visually evoked responses in alternating smus *Amer J Ophthal. 71* 1292–1297

R W (1973) The effect of lid suture upon the growth of cells in the dorsal lateral ulate nucleus of kittens *J Comp Neurol 148* 417–428

A M *McDonald W I & Mushin J (1979) Delayed pattern-evoked responses in* eurus in relation to visual acuity *Trans ophthal Soc U K 93* 315–324

) H & Wiesel T N (1963) Effects of visual deprivation on morphology and logy of cells in the cat s lateral geniculate body *J Neurophysiol. 26* 978–993

(1979) Physiological basis of amblyopia *Trends Neurosci 2* 209–212

& Wright M (1974) Is amblyopia due to inappropriate stimulation of the sustained ay during development? *Brit. J Ophthal. 58* 165–175

I & Wright M (1976) Properties of LGN cells in kittens reared with convergent t a neurophysiological demonstration of amblyopia *Exp B ain. Res 25* 63–77

Levi D M & Harwerth R S (1978) Contrast evoked potentials in strabismic and anisometropic amblyopia *Invest Ophthal 17* 571–575
von Noorden G K (1973) Histological studies of the visual system in experimental amblyopia *Invest Ophthal 12* 727–734
Parker D M & Salzen E A (1977) The spatial selectivity of early and late human visual evoked response *Perception 6* 85–95
Persson H E & Sachs Ch (1979) Visual evoked potentials during visual impairment in multiple sclerosis In Barber C (Ed) *Proceedings of the Evoked Potentials Symposium* pp 575–579 MTP Press Limited. Lancaster
Schmielau F & Singer W (1977) The role of visual cortex for binocular interactions in lateral geniculate nucleus *Brain Res 120* 354–361
Sokol S & Shaterian E T (1976) The pattern-evoked cortical potential as an index of visual function In Moore S Mein J & Stockbridge L (Eds) *Orthoptics Past Present Future* pp 59–67 Stratton New York
Spekreijse H Khoe L H & van der Tweel L H (1972) A case of amblyopia: electrophysiology and psycho-physics of luminance and contrast. In Arden G B (Ed) *The Visual System* pp 141–156 Plenum Press New York
Srebro R (1978) The visually evoked response – binocular facilitation and failure when binocular vision is disturbed *Arch Ophthal (Chicago) 96* 839–844
Tolhurst D J (1975) Sustained and transient channels in human vision *Vision Res 15* 1151–1155
Wanger P & Nilsson B Y (1978) Visual evoked responses to pattern reversal stimulation in patients with amblyopia and/or defective binocular functions *Acta Ophthal 56* 617–627
Wanger P & Persson H E (1979) unpublished observation

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THE INFLUENCE OF HYPEROSMOTIC STRESS ON THE BLOOD RETINAL BARRIER EFFECTS ON THE ELECTRORETINOGRAM

BY

PER TÖRNQUIST[1] and AVI RING

Electroretinographic recordings were obtained from cat eyes before and after an intracarotid injection of a hypertonic NaCl solution It was found that after the injection the c wave decreased in amplitude or disappeared but re appeared within a period of four to six hours suggesting that there is a reversible opening of the tight junctions following osmotic stress

Key words osmotic stress – electroretinogram – retinal pigment ep thelium – blood retinal barrier

the blood brain barrier the blood retinal barrier consists of a continuous f cells connected by tight junctions which provide a barrier to intercellular on Following osmotic stress the tight junctions can be opened thus giving a ogical increase in the permeability of the barrier (Rapoport 1970 Laties & ort 1976 Tornquist 1979) For the cerebral capillaries at least this pheno- is reversible (Rapoport et al 1972)

minary experiments on pig eyes showed that the retina was heavily stained ans blue following a severe osmotic stress due to leakage through the retinal nt epithelium (RPE) (Tornquist & Ring unpublished observation) In these ments it was further observed that the c wave of the electroretinogram which is known to originate from the RPE disappeared If there were a

d March 18 1980

reversibility of the opening of the RPE corresponding to that f ... could expect the c wave to reappear The purpose of the present ... to study the behaviour of the c wave following a hypertonic ... of moderate osmolarity

Methods

Two cats (B W about 2 5 kg) were anaesthetized with mebulmal ... ACO Sweden) The pupils were dilated by topical administration of ... (Mydriacyl® Alcon Texas) and 10% metaoxidrine (Neosynephrine® ...) to eliminate the influence of iris potentials The animals were dark adapted for ... min ERG recordings were obtained before an injection of hypertonic ... exposed ipsilateral carotid artery and then during the following 6 ... h. ... was also recorded from the contralateral eye as a control. The injection ... 2 osm solution given during 60 sec into the cannulated carotid artery ... proximally to the injection site A pump was used to maintain a constant ... blood pressure was measured in one of the femoral arteries.

Stainless steel electrodes were used one inserted into the corneal ... other partially isolated was advanced through the conjunctiva to behind the ... of the eyeball The potential variations were recorded using a differential ...

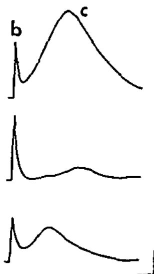


Fig 1
ERG recordings from first experiment Before (upper) ... min after ... (lower) osmotic stress Amplitude calibration 500 µV Time ...
The b- and ... waves are indicated

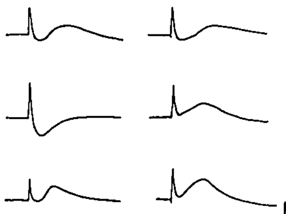


Fig 2

ordings from second experiment Left column experimental e e Right column ›e. Before (upper) 30 min after (middle) and 7 h after (lower) osmotic stress Amplitude calibration 500 µV Time calibration 0 5 sec

filter with a low frequency cut off at 0 03 Hz was used and the bandwidth was l mited Iz. The signals were amplified 1000-fold and registered on an oscilloscope screen ishes 0 5 sec in duration were obtained from a 100 W lamp (Attralux Phil ps giving an illuminance of 60 lux to the eye

Results

ked changes in the mean arterial blood pressure were observed during the of hypertonic injection The c wave decreased in amplitude after the nic injection reaching a minimal level in about 15 min (Fig 1) A gradual was noted after about 4 h In the second experiment (Fig 2) the c wave npletely abolished but began to recover gradually after about 5 h No int changes in the ERGs from the control eye (right column) could be d

Discussion

ave of the ERG originates from the RPE (Noell 1954 Braun & Wiesel 1961 et al 1977) Steinberg et al (1970) showed that the c wave is mainly ed across the apical cell membrane (facing the photoreceptors) However

the apical and the basal membranes are electrically coupled, ... pronounced hyperpolarization of the basal membrane of the RPE. The ... in hyperpolarization between the two membranes results in a ... potential which is the source of the c wave (Oakley & Green 19...

The magnitude of the c wave is affected by the presence of ... pathways through the RPE. The importance of shunt resistance f... of the c wave has been clarified by Oakley (1977). Part of the shunt ... the intracellular clefts although these clefts are partially sealed by ... complexes (Hudspeth & Yee 1973) with a low conductance ... Steinberg 1977). Oakley (1977) concluded that without the pres... change in transepithelial potential upon light stimulation and the ... would be much larger in amplitude. From this it follows that a ... barrier is a pre-requisite for obtaining a c wave in the ERG and that ... shunt resistance diminishes the c wave.

The present experiments have shown that the c wave declines or ... a 2 osm NaCl injection given into the carotid artery in cats. These ... agreement with experiments on pigs (Tornquist & Ring unpublished ... The disappearance of the c wave can be interpreted as a result of a de... resistance as discussed above. However, a secondary effect of the ... could be an enlargement of the subretinal space. This effect, which ... the c wave (Marmor 1979), cannot be excluded.

The results are also consistent with the findings of Laties & Rap... observed an increase in the permeability of the RPE to fluoresc... osmotic stress. Our observation that the alteration in the c wave ... indicates that the defects produced in the RPE heal within a few hours ... of a hyperosmolar solution on the morphology of the RPE has been ... groups arriving at somewhat different conclusions. According to Mar... the tight junctions are opened, while according to Okinami et al. (1... due to ruptured cell membranes. The reversibility observed in our ... would suggest that the trauma was relatively mild, resulting in partial ... the barrier between the cells rather than a widespread disintegration ...

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References

L T & Wiesel T N (1961) Localization of origins of electroretinogram components rareunal recording in the intact cat eye *J Physiol 158* 257–280
th A J & Yee A G (1973) The intercellular junctional complexes of retinal pigment lia *Invest Ophthal 12* 354–365
M & Rapoport S (1976) The blood-ocular barriers under osmotic stress Studies on eeze-dried eye *Arch Ophthal (Chicago) 94* 1086–1091
r M F (1979) Retinal detachment from hyperosmotic intravitreal injection *In est al 18* 1237–1244
ma Y (1976) Ultrastructural studies on the chorioretinal barrier of rabbit eye *Acta phthal Jap 80* 585–597
S & Steinberg R H (1977) Passive ionic proporties of frog retinal pigment elium *J Membrane Biol 36* 337–372
S E G Knave B & Persson H E (1977) Changes in ultrastructure and function of eep pigment epithelium and retina induced by sodium iodate II Early effects *Acta l (Kbh.) 55* 1007–1026
K (1954) The origin of the electroretinogram Amer J Ophthal 38 78 90
B H (1977) Potassium and the photoreceptor-dependent pigment epithelial hyper ization *J gen Physiol 70* 405–425
B H & Green D G (1976) Correlations of light induced changes in retinal cellular potassium concentration with c wave of the electroretinogram *J Neurophys ol* 117–1133
u S., Ohkuma M Ohta M & Tsukahara (1978) Disruption of blood retinal barrier at tinal pigment epithelium after systemic urea injection *Acta ophthal (Kbh.) 56* 27–39
rt S J (1970) Effects of concentrated solutions on blood brain barrier *Amer J l 219* 270–274
rt S J Hori M & Klatzo J (1972) Testing of a hypothesis for osmotic opening of the l-brain barrier *Amer J Physiol 223* 323–331
rg R. H Schmidt R & Brown K T (1970) Intracellular responses to light from cat ent epithelium origin of the electroretinogram c wave *Nature 227* 728 730
ust P (1979) Aspects of retinal nutrition *Acta Universitatis Upsaliensie 326* Dissertation

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FURTHER STUDIES OF THE CHEMICAL SENSITIVITY OF THE OSCILLATORY POTENTIALS OF THE ELECTRORETINOGRAM (ERG)

I GABA- and Glycine Antagonists

BY

LILLEMOR WACHTMEISTER

The oscillatory potentials (OPs) of the mudpuppy ERG were studied to evaluate the effects of GABA and glycine antagonists.
Upon exposing the retina to bicuculline and picrotoxin, blocking agents of the putative inhibitory neurotransmitter GABA all the OPs were almost abolished The earlier OPs (O_1-O_3) appeared more sensitive to the drugs than the later ones (O_4-O_5) There was no appreciable effect on the [illegible] sensitivity and saturation level of the b-wave Low concentrations of strychnine blocking the effect of the putative inhibitory neurotransmitter glycine produced a selective decrease of the amplitude of the OPs. The first (O_1) appeared less sensitive to the drug than the later ones Higher concentrations [illegible] all the OPs but also decreased the suprathreshold amplitude of the b-wave
In conclusion the present results in agreement with previous work suggest that the OPs appear to have a different origin from the b-wave and seem to be generated by inhibitory feed back circuits within retina The different sensitivity of the individual oscillatory peaks indicate that perhaps different synaptic activities might underlie the individual oscillatory potentials

Key words electroretinogram – oscillatory potentials – [illegible] GABA – and glycine antagonists mudpuppy retina.

There is now good evidence that the oscillatory potentials (OPs) of the electroretinogram (ERG) reflect possible feed back circuits in retina (Wachtmeister [illegible] 1978) First, the OPs represent radial current flows as the OPs reverse [illegible]

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microelectrode penetration Secondly the individual OPs reversed at different in retina which coupled with different timing suggest a centrifugal sequence nts to give rise to the OPs Thirdly the OPs showed a differential sensitivity to is putative neurotransmitters suggesting that the OPs are generated by an itory feed back system initiated by the amacrines Inhibitory acting neurotrans- r agents such as gamma amino butyric acid (GABA) glycine and dopamine ively depressed the OPs whereas excitatory putative neurotransmitters such as l-choline and carbacholine did not effect the OPs

ere are now five prime neurotransmitter agents which have been firmly ified to act in the inner plexiform layer (IPL) These are acetylcholine land & Ames 1976 Negishi et al 1978a) GABA and glycine (see review Neal) dopamine (Dowling & Ehinger 1975 1978) and one indolaminelike substance nger & Floren 1976 Floren 1978)

the OPs arise in inhibitory feed back synapses in the inner part of retina macological studies might allow further dissection toward determination of origin Therefore in the present report extending earlier work some sing agents of GABA and glycine were tested GABA and glycine antagonists been described to affect the amplitude of the b-wave but no systemic study of nfluence of these antagonists upon the OPs has been published (Bonaventure 1974 Pong & Graham 1976 1978 de Vries & Friedman 1977)

Methods

reparation

l experiments Necturus maculosus about 25 cm long (Sea Plantations Inc Mass USA) used The animals were kept in waterfilled aerated tanks maintained at about 6 C in a erately darkened room until they were used in experiments The water was changed dy and commercial fungicide (TetraFungi Stop Tetrawerke Melle West Germany) was d to the water to reduce the chance of infection from water mold

nimals selected for experiments were decapitated and pithed under dim red light mination provided by a microscope lamp covered by Wratten No 29 filter (Eastman ak Inc, < 0 01% < 600 nm) Following the removal of the eye the cornea, iris and lens excised to expose the entire retina The dissection was carried out under a dissecting oscope. The eye was mounted on a Ringer soaked cotton pad and placed within an ically and light shielded cage A silver sil er chloride electrode was lowered into the ous humour which was viewed in dim light under a microscope Thereafter the retina allowed to dark adapt for about 5-10 min

ecording system

ERG was recorded between an indifferent electrode behind the eye and an active trode in the vitreous The active electrode was a silver-silver chloride wire insulated to its

up with lacquer The reference electrode was a coiled silver [illegible] potentials were fed into an ac-coupled preamplifier (Neurolog NL [illegible]) [illegible] an input resistence of $10^9\Omega$ Coupling constants of either 1.5 sec or [illegible] high frequency cut-off response was set either at 10 kHz (using a [illegible]) (using a short time constant) The signals were displayed on one of the [illegible] oscilloscope (Tektronix type 5115) and photographed by an [illegible] type C 5 A) The sweep of the storage oscilloscope was synchronized with the [illegible] shutter of the photostimulator by a triggering circuit. Signals from [illegible] indicated stimulus duration were amplified and displayed on the second [illegible]

The amplitudes of the a and b-waves and the individual OPs were measured [illegible] from the photographic records The amplitude of the OPs were measured [illegible] drawn between successive troughs of the wavelets and expressed in arbitrary [illegible] amplitude of the b-wave was measured from the baseline but virtually [illegible] obtained when the b-wave was measured from the a wave trough The [illegible] individual OPs a and b-waves were measured from stimulus onset to the peak [illegible] individual oscillatory peaks b-wave or negative a wave

c Photostimulator

Stimulus light was obtained from a xenon arc lamp (Osram XBO [illegible]). The output (Log O) of the system was 1 17 × 10^{20} photons cm^2 sec measured by [illegible] Universal Photometer The stimulus beam was focused on the retina by [illegible] system and covered the whole eye-cup Intensity of the light beam was [illegible] density filters Stimulus duration was regulated by an electromagnetic shutter [illegible] Vincent Lab Inc) Flashes of 75 msec duration delivered at a constant interval [illegible] used

d Solutions

The drugs were dissolved in an amphibian Ringers solution (6.5 g NaCl [illegible] 0 14 g KCl 0 16 g $CaCl_2$ 0 5 g hepes/l) and the pH was adjusted to 6.9 [illegible] between 0 001 mM to 10 mM were tested except for bicuculline and picrotoxin [illegible] were either not soluble in 10 mM solutions (picrotoxin) or could not be [illegible] keeping an acceptable pH (bicuculline) The control Ringers and the Ringer [illegible] dissolved drug were held in micrometer syringes (Gilmont) which were [illegible] tubings Glass micropipettes with tips of 50-100 µ were connected to the [illegible] tubings The micropipettes were mounted on micromanipulators [illegible] facilitate positioning of their tips close to the vitreous surface With this [illegible] about 4 µl could be delivered to the retinal surface The concentrations [illegible] concentrations applied and not effective concentrations at recording [illegible] summerized below are drawn from observations obtained from a total of [illegible]

Results

A. Effects of bicuculline and pictrotoxin

Fig 1 A illustrates the ERG in response to full field flashes of [illegible] msec [illegible] an interstimulus interval of 30 sec before the administration of [illegible]

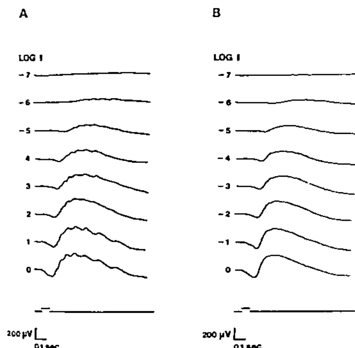
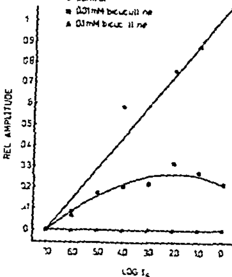


Fig 1

ecorded with a long time constant (τ = 1 5 sec) in response to full field stimulus of 75 luration and of different intensities delivered at an interval of 30 sec A Before the ition of bicuculline B The effect of 0 1 mM bicuculline on the OPs a and b-wave of RG The effect appeared within 1 min after the drug was added and gradually sed reaching a maximum at about 2 5 min when these recordings were taken A selective suppression of the OPs occurred

tude OPs could be identified superimposed on the b-wave at intensities as low -6 0 In response to high intensity flashes the OPs are readily observable Two ifter the retina was exposed to 0 1 mM bicuculline all the OPs were selectively hed from the b-wave which is clearly seen when the response sets of Fig 1 A 3 are compared In contrast the amplitudes of the a and b-wave were not d (Fig 1 B)

e V (summed amplitude of the OPs)/Log I (stimulus light intensity) function 5 2 A depicts that the summed amplitude of the OPs increased linearly over a of 6 log units There was a linear augmentation of the b-wave over a range of units beyond which the amplitude levelled off (Fig 2 B) The a wave increased rily over the range used in these experiments (Fig 2 B)



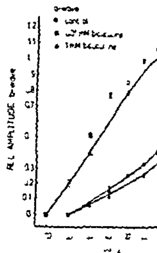
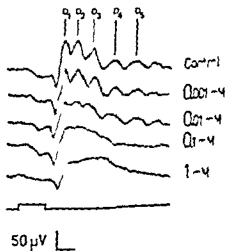


Fig 2

Stimulus-response curves of the OPs a and b-waves of the ERG before a... of bicuculline A Relative summed amplitude of the OPs of the ERG. 0.01 m... selectively supressed the OPs Higher concentrations (0.1 mM) abolished all the ... lative amplitudes of the a and b-waves The V/Log I curve of the b... unaltered when bicuculline (0.01 mM) was applied High concentra... decreased the suprathreshold a wave



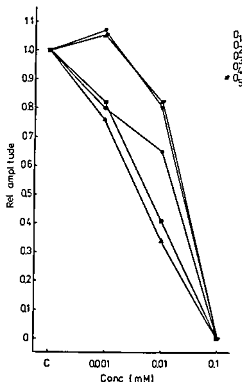


Fig 4

ve amplitudes of the individual oscillatory peaks in relation to different concentrations uculline The amplitudes are measured from the ERG s shown in Fig 3 The earlier OPs O_3) appeared more sensitive to the drug than the later ones (O_4 and O_5) All the OPs were abolished when 0 1 mM bicuculline was applied

, 2 illustrates the effect of different concentrations of bicuculline on the ulus-response functions of the OPs a and b-waves A low concentration of ulline (0 01 mM) dramatically reduced the OPs (Fig 2 A) whereas the V/Log I tions of the a and b waves were virtually unaltered (Fig 2 B) Only a very slight ase of the maximum amplitude of the b-wave was observed after the ication of bicuculline There was no appreciable change of threshold sensitivity e a and b-waves

1 mM of bicuculline extinguished all the OPs (Fig 2 A) When higher concen ons of bicuculline (1 mM) was used a slight decrease of the amplitude of the athreshold a wave was observed (Fig 2 B)

g 3 shows the differential effect of bicuculline on the individual oscillatory s Low concentrations of bicuculline (0 001 mM and 0 01 mM) selectively and

have been disrupted either by saturation of GABA receptor ... tion of GABA or by blocking the action of GABA by the ... or picrotoxin

Laminar profile studies of the mudpuppy retina have ... have their origin in feed back circuits in the inner part of ... Dowling 1978) The present findings may therefore reflect ... properties of these neural pathways These neural pathways ... dependent

The oscillations on the decaying slope of the on transient of the ... response (PNR) an extracellular potential recorded in the ... been shown to decrease in amplitude after treatment with GAB (Burkhardt 1972 Mooney 1978) A negative feed back ... amacrine junction has been suggested to be GABA mediated ... (Burkhardt 1972) There is now also morphological evidence ... interplexiform cell in the cat retina which constitutes another ... circuitry of retina (Nakamura et al 1979) Recent electrophys... indicate that GABA may play a role in a feed-back synapse between ... cells and the cones in the cyprinid retina (Wu & Dowling 19...). The feed back circuits responsible for the OPs seem to share this GABA ... other proposed feed back pathways in the retina

Another finding of interest is that the OPs were selectively ... concentrations of the convulsant strychnine Strychnine antagonizes the longer amino acid glycine (Eccles 1964 Curtis et al. ... 1972 Mooney 1978) Thus the effect upon the OPs may be due ... antagonism of the glycine network within the retina.

In a previous study on the mudpuppy retina it was shown that ... selectively reduced when glycine was added to the open eye cup ... Dowling 1978) By analogy with the GABA bicuculline results ... pathways may have been inactivated either by saturating the gly... application of glycine or by blocking the effect by the administration ...

Histochemical as well as physiological studies have suggested ... probably an inhibitory synaptic transmitter and strychnine ... blocking agent of glycine in the IPL of retina (see review Neal ...) ... present results support a previous proposal that only inhibitory feed ... are involved in the generation of the OPs (Wachtmeister & Dowling ...)

Recently it has been suggested that glycine also may be involved ... pathways which mediate the red light response of the C-type horizontal ... carp retina (Wu & Dowling 1979 Belgum & McReynolds 19...). This ... that the OPs might reflect synaptic activity in the outer plexiform ... such an interpretation is not compatible with the behaviour of ...

tudies (Wachtmeister & Dowling 1978) and is unlikely On the other hand orphological studies have indicated the existence of glycinergic inter cells in the goldfish retina (Marc et al 1979) The activity of such a pathway would then be more suggestive to underlie some of the potentials

r observation to be emphasized is the selective and differential sensitivity s First the OPs were selectively decreased or even abolished whereas the is hardly affected Thus the present findings reinforce the idea that the of the b-wave is different from the OPs which suggests different origin of e compared to the OPs Secondly the later OPs (O_4-O_5) were less sensitive antagonists than the earlier ones (O_1-O_3) The first OP(O_1) was less o the glycine antagonist than the later ones (O_2-O_4) It has been shown epolarizing biopolar cells and the on response of the on-off amacrine cells A sensitive whereas the hyperpolarizing bipolar cells were more glycine (Miller & Dacheux 1976 Miller et al 1977) Glycine has also been ated to selectively depress the off-discharge of the on-off cells and certain of the carp retina leaving the on-discharge unaffected (Negishi et al he existence of separate GABA and glycine releasing amacrine cells has suggested (Miller et al 1977) Picrotoxin has been demonstrated to block electively whereas strychnine was shown to block some features of other ganglion cells (Wyatt & Daw 1976) Picrotoxin has also been shown to ie receptive field size of both sustained and transient on-off ganglion cells glycine altered the temporal organization abolishing the off discharge of f response in the frog retina (Bonaventure & Wioland 1978) Thus the al sensitivity of the OPs may suggest that perhaps chemically different ictivities underlie the individual oscillatory peaks

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References

& Mc Reynolds J (1979) Synaptic transmission in the outer plexiform layer of the is retina. Abstracts of ARVO-Meeting Sarasota USA

ure N., Wioland N & Mandel P (1974) Antagonists of the putative inhibitory tter effects of taurine and GABA in the retina. *B a n Res 80* 281–289

Bonaventure N & Wioland N (1978) Amino acids implication in the ... receptive field organization Abstracts of the second European ... Florence Italy
Burkhardt D A (1972) Effects of picrotoxin and strychnine upon electrical ... proximal retina *Brain Res 43* 246–249
Curtis D R Hosli L & Johnston G A R (1968a) The hyperpolarization of ... motorneurones by glycine and related amino acids *Exp Brain Res 5* 35 ...
Curtis D R Hosli L & Johnston G A R (1968b) A pharmacological study of the ... of spinal neurones by glycine and related amino acids *Exp Brain Res 6* 1 ...
Curtis D R (1968c) Pharmacology and neurochemistry of mammalian central ... processes In C von Euler S Skoglund & U Soderberg (Eds) ... Inhibitory Neuronal Mechanisms Pergamon Press Oxford 4?9 ...
Curtis D R Duggan A W & Johnston G A R (1969) Glycine strychnine, ... spinal inhibition *Brain Res 14* 759–762
Curtis D R Duggan A W Felix D Johnston G A R & Mc Lennan H (19?1) ... between bicuculline and GABA in the cat brain *Brain Res 33* 5...
Dowling J & Ehinger B (1975) Synaptic organization of the dopamine contain... form cells of the goldfish and Cebus monkey retina *Science 188* ...
Dowling J & Ehinger B (1978) The interplexiform cell system I Synapses of the d... gic neurons of the goldfish retina *Proc roy Soc B 201* 7–?6
Eccles J C (1964) The Physiology of Synapses pp 189–?00 Academic Press, New ... 189–200
Ehinger B & Floren I (1976) Indolamine accumulating neurons in the retina of ... and goldfish *Cell Tiss Res 175* 37–48
Floren I (1978) Indolamine Accumulating Neurons in the Retina. Thesis. Lund ... Lund Sweden
Kawaguchi S & Ono T (1973) Bicuculline and picrotoxin sensitive inhibition in ... neurones of cat *Brain Res 58* 260–?65
Marc R Lam D & Stell W (1979) Glycinergic pathways in the goldfish retina. Abs... ARVO meeting Sarasota USA
Masland R & Ames A (1976) Response to acetylcholine of ganglion cells in an ... mammalian retina *J Neurophysiol 39* 1220–1?35
Miller R & Dacheux R (1976) GABA mediated neuronal mechanisms in the ... retina Abstracts of Neuroscience Toronto
Miller R Dacheux R & Frumkes T (1977) Amacrine cells in Necturus Retina: E... independent γ amino butryc acid and glycine releasing neurons *Science 198* ...
Mooney R D (1978) GABA mediated control of transient signals in the inner ret... *Res 145* 97–115
Nakamura Y Mc Curie B & Sterling P (19?9) Selective uptake of [^{3}H] γ amino buty... (GABA) and [^{3}H] γ glycine by neurons of the amacrine layer of cat retina. Abs... Neuroscience Meeting Toronto
Neal M (1976) Amino acid transmitter substances in the vertebrate retina. ... *Pharmacol 7* 321–332
Negishi K Kato S Teranishi T & Laufer M (19?8a) An electrophysiological study ... cholinergic system in the carp retina *Brain Res 148* 67–84
Negishi K Kato S Teranishi T & Laufer M (19?8b) Dual actions of some amino a... spike discharges in the carp retina *Brain Res 148* 67–84

K. Kato S & Sugawara K (1978c) Effects of locally applied chemicals on transretinal
al and horisontal cells in the isolated carp retina. *Pflugers Arch. 375* 53–60
F & Graham L. T (1976) A relatively simple differential screening test for GABA or
antagonists using rat electroretinography *Arch Int. Pharmacodyn 220* 275 286
F & Graham L. T (1978) Effect of strychnine on the rat electroretinogram *J Pharm.
col. 30* 327–328
ester L. & Dowling J (1978) The oscillatory potentials of the mudpuppy retina
Ophthal Vis Sci. 17 1176–1188
G & Friedman A (1978) GABA picrotoxin and retinal sensitivity *Brain Res 48*
135
Dowling J (1979) Effects of GABA and glycine on the cyprined retina Abstracts of
) Meeting Sarasota USA
& Daw N (1976) Specific effects of neurotransmitter antagon sts on ganglion cells
nt retina *Science 191* 204–205

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THE ALTERATION AND ASYMMETRY OF CUP AND DISC DIAMETERS

BY

BO BENGTSSON

Increases in cupping with time and differences in cup size between the eyes of one person were studied in a material derived from a gen ophthalmic population survey Cup and disc diameters were measured fundus photographs The effect of refraction on the magnification of eye camera system was compensated for by the use of a simple correct factor

The disc diameter increased slowly but steadily with advancing years but rim area remained unaffected and as a consequence the rim breadth dimini hed The increase in disc diameter and the decrease in rim breadth com to cause a marked increase in cup diameter with ageing

A multiple regression analysis showed cup diameters to be independent of refraction as well as of systemic blood pressure and only weakly associated intraocular pressure

Side differences in cup diameter were strongly dependent on side differences in disc diameter

Some implications of these findings were briefly discussed

Key words cup diameter – disc diameter – age – intraocular pressure – s blood pressure – refraction

Theodore Schwartz et al (1975) last emphasized that the physiological cup of normal eye is not a static structure and that greater understanding of changes in this least studied affiliate of the glaucoma triad is needed New for detection of minor changes in the optic disc by comparison of photographs (Goldmann & Lotmar 1977 1978 1979 Bengtsson & K

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) have renewed our interest in this field The present reinvestigation of existing cross sectional data (Bengtsson 1976) was undertaken as a prelimin iore time-consuming prospective studies

Material

aterial was derived from a general ophthalmic population survey carried out Dalby Community Care Centre in southern Sweden from March 1969 to 9/0 Based on a directory invitations were mailed to all persons aged eight r more who had been resident since December 1968 in the suburban village nding the centre Out of 1917 persons invited 1702 (88 8%) took part in the

ur of fundus photographs was filed in 1620 cases but reliable measurements and disc sizes were obtained from no more than 2334 phakic eyes in 1322 six eyes in four patients with suspected or manifest glaucoma were excluded he present study A complete set of data was obtained for 2274 eyes in 1287 ts

Methods

iann tonometry sphygmomanometric measurement of the systemic blood re subjective refraction in cycloplegia and fundus photography were attemp- every subject. Conventional equipment was used according to a fixed imme

ression analysis was carried out with two standard computer programmes – and SPSS

fundus photographs were taken by an assistant using the modern Zeiss s camera with *standard magnification (2 5 ×) and Kodachrome II film for* transparencies (24 × 36 mm) The *astigmatism-correcting device was not* nd the *camera-extension was preadjusted to the refraction of the eye under* gation (Bengtsson & Krakau 1977)

slides were projected on to a screen at a fixed *magnification (16 ×) and* ired on ruled paper by the author *Not only differences in colour between the* nd the rim but also other features *such as deflections of the vessels were* into account when estimating the amount of *cupping of the optic nerve head* ieasurements were expressed in *arbitrary units approximately equivalent to* nm. The geometrical mean *of the vertical and the horizontal diameter was* to describe the size of cups and discs *The effect of refraction on the*

magnification of the eye-camera system was compensated for by the use of a [illegible] correcting factor (Bengtsson & Krakau 1977). In non-excavated discs, the [illegible] vessels were considered equivalent to a cup with a diameter of two units.

Results

I Alteration of the optic nerve head with advancing years

The observed disc diameter (d) and cup diameter (c) were used to cal[illegible] double rim breadth (d c) as well as the compact-disc diameter ($\sqrt{d^2-c^2}$) [illegible] diameter of a circle with the same area as the rim. Changes in the mean of [illegible]

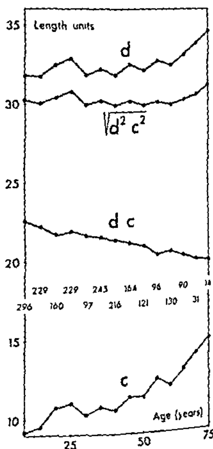


Fig 1

Changes in disc diameter (d), cup diameter (c), compact-disc diameter ($\sqrt{d^2-c^2}$) [illegible] double rim breadth (d−c) with advancing years. The circles represent the mean [illegible] numbers the number of observations in each class. One arbitrary length unit is approxima[illegible]vely equivalent to 0.05 mm.

parameters with advancing years in the present material were illustrated in With the exception of probably insignificant deviations in subjects in their es and seventies a more or less linear relationship with age was indicated The disc diameter increased slowly with advancing years but the mean compact iameter remained unaffected and the mean double rim breadth decreased geing *The changes in disc diameter and rim breadth combined to cause a* d increase in mean cup diameter with age

: average increase in disc diameter was 0 02 arbitrary units/year The average ase in double rim breadth was 0 04 units/year and accordingly the average se in cup diameter 0 06 units/year In other words the mean cup diameter sed from about 0 5 mm at 10 to about 0 75 mm at 75 years of age

lt ple regression analysis of variations in cup size

isc diameter was independent of the intraocular pressure and the refraction facts that cup diameters are unevenly distributed (Bengtsson 1976) and ident of age had however to be taken into account in a study of factors more tely associated with cup size We therefore used a stepwise multiple regression sis in which disc diameter and age were included together with the intraocular ure (IOP) the systolic blood pressure (SBP) and the refraction (REF) as endent variables

ien diameters and age had been added to the regression equation the partial

Table I

Partial coefficients of association with cup diameter

Independent variable	Partial coefficients of	
	Regression	Correlation
Entered		
d	1 16 ($P < 0\ 001$)	–
age	0 04 ($P < 0\ 001$)	–
Not entered		
IOP	–	0 08 ($P < 0\ 01$)
REF	–	0 05 ($P > 0\ 05$)
SBP	–	0 01 ($P > 0\ 05$)

into the regression equation

d = disc diameter IOP = intraocular pressure REF = refraction
SBP = systolic blood pressure

Table II

Observed and corrected variances and coefficients of association between cup and disc for diameters and their differences

	Observed values for		Corrected values	
	Diameters	Differences	Diameters	[illegible]
Cup variance (V_c)	26 0	7 0	[illegible]	[illegible]
Disc variance (V_d)	11 6	4 9	10 8	[illegible]
$\sqrt{V_c \times V_d}$	17 4	5 4	16 6	[illegible]
Regression of cup on disc	1 18	0 77	[illegible]	[illegible]
Cup disc correlation	0 79	0 59	0 85	[illegible]

Corrected variance = observed variance × correlation between repeated measurements
Corrected coefficient = observed coefficient × observed variance corrected variance
(The pertinent variance is V_d for the regression of cup on disc and $\sqrt{V_c \times V_d}$ for the cup-disc correlation)

correlations of systolic blood pressure and refraction with cup diameters insignificant and that of the intraocular pressure very low even if statistically significant (Table I)

By the examination of residuals product terms subsamples and polynomial approximations it was possible to exclude major non linear and non-additive relationships

The regression equation after the second step

$$c = 1\ 16d + 0\ 04 \times \text{age (in years)} + e - 28\ 1 \text{ units}$$

(in which e stands for a normally distributed error term – the cup disc residual) was therefore considered to give a reasonably accurate description of variations in cup size observed in the present material

III Side differences in cup and disc size

Two diameters are needed to determine one side difference but side differences are less dispersed than diameters The proportion of the observed variance due to errors of measurement is therefore much larger for side differences in diameters than for the diameters themselves We therefore used the correlation between repeated measurements (0 93 for d and 0 98 for c) to estimate corrected variances as well as coefficients corrected for attenuation in addition to the observed ones (Table II)

Even after such correction the standard deviation of the difference between right and left diameter was about 50% of that for the diameters themselves

ent was equally valid for cups and discs (Table II) After correction for tion by errors of measurement the coefficients describing the covariation n cup and disc sizes were almost exactly the same for side differences in er as for the diameters themselves In this respect therefore inter and dual variations seem to follow the same rules

Discussion

is investigators are said to have reported mixed findings with respect to an ect on the cup-disc ratio and it is generally taught that cupping does not with age (For references see Schwartz et al 1975) A closer scrutiny shows r that all earlier reports in the literature agree with the present one in ing an apparent increase in cup size with age even if this trend has not always tatistical tests for significance

use of the cup-disc ratio to describe the size of the cup is based on the otion that the size of the disc is constant. An increase in cup-disc ratio has ore seemed to imply a loss of neural tissue difficult to accept in normal eyes

results of a cross-sectional study like the present one can reflect no more verages of changes in the population and the range and time-course of ual changes in cup and disc sizes remain largely unknown It is however lt to avoid the following interpretation of Fig 1

re is normally no loss or gain of neural tissue and the area of the rim remains cted by age There is however a slow but steady increase in size of (a ty of) all discs A small increase in disc diameter gives a relatively large se in disc area necessitating the same increase in cup area in order to leave the ea unaffected Since the area of the cup is much smaller than the area of the e resulting change in cup diameter is larger than the change in disc diameter onsequence the rim breadth decreases when the disc diameter increases

amount of tissue thus remains constant in a certain mature nerve head but it ary between different discs and the combined effects of all influences ling age) leave the rim breadth (rather than the rim area) largely independent size (Bengtsson 1976) The multiple regression equation

$$c = 1\ 16\,d + 0\ 04 \times \text{age} + e - 28\ 1 \text{ units}$$

erefore be interpreted to mean that changes in cup diameter in general more parallel those in disc diameter but that ageing also results in a decrease in eadth that should be taken into account

apparent similarity of cup-disc relations valid for side differences in ter to those valid for diameters themselves seems remarkable in view of the

opinion that cup and disc diameters are to a great extent inherited [illegible] 1980) while their side differences cannot be inherited at all

Kessing & Gregersen (1977) have reported a pressure-conditioned [illegible] the disc causing reversible cupping in early stages of congenital glaucoma [illegible] results gave no reason to believe that the increase in disc and cup diameters [illegible] reported here could be regarded as an effect of the intraocular pressure [illegible] disc is distended by normal pressures in the adult. The changes in cup [illegible] intraocular pressure were however not cumulative and therefore not [illegible] irreversible

The possibility of an aquired enlargement of the optic cup without an [illegible] nerve tissue reported here calls attention to a similar possibility of cav[illegible] degeneration with extensive loss of nerve fibers in the total absence of [illegible] of the optic nerve head (Schnabel 1905) It appears that neither an enlarg[illegible] nor a diminishing rim breadth should be considered pathognomonic of glauco[illegible] tous disease Our search for the first signs of glaucomatous damage should [illegible] be redirected from the documentation of changes in cup size toward early detec[illegible] of cavernous degeneration

References

Bengtsson B (1976) The variation and covariation of cup and disc diameters [illegible] (Kbh) 54 804–818

Bengtsson B (1980) The inheritance and development of cup and disc diameters [illegible] ophthal (Kbh) 58 733–739

Bengtsson B & Krakau C E T (1977) Some essential optical features of the Zeiss [illegible] camera *Acta ophthal (Kbh) 55* 123–131

Bengtsson B & Krakau C E T (1979a) A simple routine for optic disc photography [illegible] a natural pupil *Acta ophthal (Kbh) 57* 151–154

Bengtsson B & Krakau C E T (1979b) Flicker comparison of fundus photographs [illegible] *ophthal (Kbh) 57* 503–506

Goldmann H & Lotmar W (1977) Rapid detection of changes in the optic disc stereo[illegible] noscopy *Albrecht v Graefes Arch klin exp Ophthal 202* 87–99

Goldmann H & Lotmar W (1978) Rapid detection of changes in the optic disc ster[illegible] noscopy II *Albrecht v Graefes Arch klin exp Ophthal 205* 263–277

Goldmann H & Lotmar W (1979) Rapid detection of changes in the optic disc stereo[illegible] noscopy III *Albrecht v Graefes Arch klin exp Ophthal 211* 243–249

Kessing Sv V & Gregersen E (1977) The distended disc in early stages of con[illegible] glaucoma *Acta ophthal (Kbh) 55* 431–435

Schnabel W J (1905) Die Entwicklungsgeschichte der glaukomatösen Exka[illegible] Augenheilk 14 1–22

Schwartz J T Reuling F H & Garrison R J (1975) Aquired cupping of the optic nerve [illegible] in normotensive eyes *Brit J Ophthal 59* 216–222

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THE INHERITANCE AND DEVELOPMENT OF CUP AND DISC DIAMETERS

BY

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The familial resemblances in disc diameter (d) and cup diameter residual (e) were studied in 845 individuals forming 297 families and 1040 pairs of spouses and first-degree relatives The cup diameter residual was computed as the difference between the observed cup diameter and the cup diameter expected from the disc diameter and the age according to a multiple regression equation The results for d and e were similar Spouses did not resemble each other at all The resemblance between first-degree relatives on the other hand was quite substantial There were no major influences of sex linkage dominance or common environment and no obvious maternal effects It was concluded that the familial resemblance was essentially additively genetic in origin The heritability was estimated at 2/3 The remaining variance was attributed to errors of development The results can be applied to other surface dimensions of the optic nerve head

Key words familial resemblance – cup diameter – disc diameter – heritability – development

rejudiced analysis of the familial resemblance has led to doubts concerning the ditary nature of the intraocular pressure (Bengtsson 1976a) and the blood sure (Bengtsson et al 1980) The finding of an apparent similarity between the disc relation for side differences in diameter and that for the diameters nselves (Bengtsson 1980) alerted us to the possibility that the hereditary nature ie diameters should be doubted too

he prevailing opinion that the size of the optic cup is inherited dates back to lies on the genetic determination of the cup-disc ratio (For references see wartz et al 1975) The use of the cup-disc ratio was based on the assumption

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that the size of the disc is constant The determination of the c [illegible] therefore seemed equivalent to the determination of all essential d [illegible] *optic nerve head* The size of the optic disc is not constant, however and [illegible] cup sizes have to be measured separately in order to determine elementary [illegible] dimensions of the optic nerve head

Cup diameters are unevenly distributed and heavily dependent on the [illegible] age (Bengtsson 1976b 1980) They had therefore to be transformed [illegible] present purpose To this end we used a multiple regression analysis to c[illegible] expected cup diameters from disc diameters and age The differences be[illegible] observed and expected cup diameters i e *the cup diameter residuals, are norm[illegible] distributed* and (by definition) independent of disc size and age The [illegible] kinds of influences (errors of measurement included) not common to cup and [illegible] diameters

We therefore decided to analyse the familial resemblance in disc diamete[illegible] cup diameter residual

The total (phenotypic) variance V_P of a measurable property may be regarded as [illegible] of separate causal components e g the additive genetic variance (V_A) the [illegible] dominance (V_D) and environmental variance (V_E)

$$V_P = V_A + V_D + V_E +$$

The heritability (h^2) is defined as the ratio of additive genetic to phenotypic variance

$$h^2 = V_A/V_P$$

Parts of some causal components are common to certain family members Th[illegible] relatives and spouses to co vary i e to resemble each other The covariance is depen[illegible] the type of relationship

$$\text{covariance}_{\text{Husband Wife}} = \text{common } V_E$$
$$\text{covariance}_{\text{Parent-Child}} = \text{common } V_E + 0.5\, V_A$$
$$\text{covariance}_{\text{Sibling Sibling}} = \text{common } V_E + 0.5\, V_A + 0.25\, V_D$$

The degree of resemblance is usually expressed in terms of the covariance as a pr[illegible] the phenotypic variance i e as the regression (or correlation) coefficient

$$b\ (\approx r) = \text{covariance}/V_P$$

where V_P refers to the variance of the independent pair member (for b) or to the g[illegible] mean of the variances of both members (for r)

If the covariance caused by common environment and dominance is so small a[illegible] negligible the regression of children on one parent (b_{OP}) and the correlation bet[illegible] (r_{FS}) become equal to half the heritability

$$b_{OP} = r_{FS} \sim 0.5\ V_A/V_P = 0.5\ h^2$$

In this case the degree of resemblance provides a quantitative estimate of the herita[illegible]

Material

naterial was derived from a general ophthalmic population survey carried out
. Dalby Community Care Centre in southern Sweden from March 1969 to
19/0 (Bengtsson 1976b 1980)

e official identification numbers of the eldest sibling and the eldest child of
_ person were requested in a questionnaire and orally verified at the examina
, In accordance with these data 297 families consisting of 845 individuals with
ole measurements of cup and disc sizes were assembled and pairs of first
ee relatives and spouses constructed as detailed later

ily one eye (preferably the left) from each subject was used to estimate the
ee of familial resemblance

Methods

and disc diameters were measured on fundus photographs (Bengtsson 1976b
) Bengtsson & Krakau 1977)

he cup diameter residuals (e) were computed from the observed cup diameter
the disc diameter (d) and the age (in years) of the subject according to the
owing equation

$$c = 1\ 16d + 0\ 04 \times age + e - 28\ 1$$

ained by a multiple regression analysis of the initial material (Bengtsson 1980)

o describe the degree of familial resemblance we calculated both correlation
l regression coefficients All pairs consisted of two individuals The part of the
ependent member of a pair was always assigned to the older relative and to the
le spouse Spouses were included only if they had at least one examined child
ether Otherwise we used all pairs that could be constructed in order to obtain
greatest possible precision within the limitations imposed by the already existing
aterial One person might therefore be a member of two families and could
pear both as child and as sibling in one of these The number of fully
lependent observations in our groups was accordingly less than might be
erred from the number of pairs

The probability that observed values or their differences had arisen by chance
is estimated after z transformation of the correlation coefficients Only fully
dependent pairs were counted to ascertain that the coefficients were significant
it the total number of pairs was used to ascertain that the differences were not
gnificant

Results

The results for d and e were similar and will therefore be described together

The coefficients describing the resemblance between spouses were insignificant or negative The coefficients describing the resemblance between pairs within the seven fundamental groups of first degree relatives on the other hand were positive and with few exceptions (the coefficients describing the resemblance in disc diameter between brothers and that in cup diameter residual between mothers and their sons) statistically significant (Table I)

The differences between pairs of father son and pairs of mother-daughter, between pairs of father-daughter and pairs of mother son as well as between pairs of brothers and pairs of sisters were not significant The remaining differences between the coefficients of the seven fundamental groups of first-degree relatives were of the same order of magnitude as those just mentioned. Their statistical significance could not easily be tested however since the involved groups were composed of the same individuals to such an extent that they had to be considered dependent on each other The observed directions of the differences were opposite to those expected from sex linkage We therefore felt free to per-

Table I

Familial resemblance in disc diameter (d) and cup diameter residual (e)
(r = correlation coefficient b = regression coefficient)

	Number of pairs	d		e	
		r	b	r	b
Fundamental groups					
Husband – wife	149	0.02	[illegible]	[illegible]	–0.13
Father – son	158	0.39	0.41	[illegible]	[illegible]
Father – daugther	133	0.24	[illegible]	[illegible]	[illegible]
Mother – son	191	[illegible]	0.30	[illegible]	[illegible]
Mother – daugther	165	0.41	0.36	0.30	[illegible]
Brother – brother	77	0.11	[illegible]	0.38	[illegible]
Sister – sister	48	[illegible]	0.36	0.34	[illegible]
Brother – sister	119	[illegible]	[illegible]	0.19	
Composite groups					
Father – child	291	0.33	0.34	[illegible]	[illegible]
Mother – child	356	0.31	0.34	[illegible]	[illegible]
Sibling – sibling	244	[illegible]	0.22	[illegible]	

Table II

The heritability (h^2) of the disc diameter (d) and the cup diameter residual (e) estimated from observed and corrected values pertaining to the regression of children on their parents (b_{OP}) and the full-sib correlation (r_{FS})

	Observed values for		Corrected values for	
	d	e	d	e
V_p of parents	11.2	8.2	10.4	6.6
$2b_{OP}$ (n = 647)	0.68	0.50	0.73	0.62
V_p of siblings	13.1	9.3	12.3	7.7
$2r_{FS}$ (n = 244)	0.42	0.54	0.45	0.65
Pooled estimate of h^2	0.61	0.51	0.65	0.63

Corrected V_P = observed $V_P - V_M$

Corrected coefficient = observed coefficient × $\frac{\text{observed } V_P}{\text{corrected } V_P}$

Pooled estimate of $h^2 = (2b_{OP} \times 647 + 2r_{FS} \times 244)/891$

ng of the six fundamental groups of first-degree relatives into three major s (father-child, mother-child and siblings) in order to obtain an optimal ate of the overall resemblance within each one of them (Table I)

disc diameters the full sib correlation seemed somewhat smaller than the ations between parents and their children. For cup diameter residuals the e of resemblance was about the same in all three major groups of relatives e I)

discussed later these findings suggested that the familial resemblance in d and essentially additively genetic in origin. The regression of children on their ts and the full sib correlation could therefore be used to estimate the ability, i.e. *the ratio of additive genetic variance to phenotypic variance (Table*

e variances due to errors in measurement of the disc diameter (V_{Md} = 0.8) and diameter (V_{Mc} = 0.5) *were determined by repeated measurements on a limited* ber of slides and used to calculate the variance due to errors of measurement in up diameter residual ($V_{Me} = V_{Mc} + 1.16^2 \times V_{Md}$ = 1.6) and thereafter to ct the observed variances and coefficients of association (Table II)

In order to get a single estimate of the heritability based on the [illegible] information we pooled the two different estimates of the same heritability [illegible] that took account of the number of pairs of first-degree relatives used [illegible] each one of them (Table II)

Discussion

The principal feature of the results reported here was of course [illegible] difference between spouses and first-degree relatives Spouses did [illegible] each other at all The resemblance between first-degree relatives, on the [illegible] hand was quite substantial

The disparities between different groups of first-degree relatives seemed [illegible] ficant and gave no reason to suspect much sex linkage There were no [illegible] of marked dominance obvious maternal effect or strong influences from [illegible] environment. We therefore concluded that the observed familial [illegible] disc diameter and cup diameter residual was essentially additively genetic [illegible]

The coefficients of association are attenuated by errors in measurement [illegible] which inflate the variances but leave the covariances unaffected. The [illegible] inflated not only by the original errors in c but also by the errors in d, [illegible] reinforced (× 1 16) and transmitted to e via the expected cup diameter [illegible] coefficients for e are therefore more attenuated than those for d [illegible] correlataion between repeated measurements on the same slide (0 95 for d [illegible] for c) we would expect nearly 2/3 of the "true" variance in both disc [illegible] cup diameter residual to be inherited (Table II)

The finding that the disc diameter and the cup diameter residual are [illegible] about the same degree implies of course that other surface dimensions [illegible] derived from them – like the expected cup diameter the cup diameter [illegible] breadth and the cup-disc ratio – are also inherited to that degree The [illegible] study therefore confirms earlier studies on the determination of the cup [illegible] (Schwartz et al 1975)

The remaining 1/3 of the variance is by definition "environmental" [illegible] not necessarily in the common meaning of the word Properties of [illegible] anatomical structures are not easily affected by circumstances extern[illegible] individual and the non genetic variation in dimensions of the optic [illegible] should probably be attributed to "errors" of development and [illegible] apparent absence of common environmental influences reported here [illegible] presence of marked side differences reported elsewhere (Bengtsson [illegible] point in that direction Small rim breadths in eyes with signs of previous [illegible]

engtsson 1976) and high cup-disc ratio in ex prematures (Fledelius 1978) cited as examples of such "errors" of development.

findings in one and the same population of results indicating external amental influences on the intraocular pressure (Bengtsson 1976) maternal on the blood pressure (Bengtsson et al 1979) and errors in development of tic nerve head (inferred here) demonstrate the potential usefulness of the ds applied here and suggest that a comprehensive analysis of the familial olance should be considered fundamental to the epidemiological study of any rable property

References

son B (1976a) Resemblance between tonometer readings on relatives and spouses *phthal (Kbh.) 54* 27–40

son B (19 6b) The variation and covariation of cup and disc diameters *Acta ophthal)54* 804–818

sson B (1980) The alteration and asymmetry of cup and disc diameters *Acta ophthal.)58* 7°6–739

sson B & Krakau C E. T (1977) Some essential optical features of the Zeiss fundus era. *Acta ophthal (Kbh.) 55* 123–131

sson B Thulin T & Schersten B (1979) Familial resemblance in blood pressure – a ernal effect? *Clin. Sci. 57* 2 9s–281s

ius H (19 8) Optic disc cupping and prematurity *Acta ophthal (Kbh.) 56* 563–573

itz J T Reuling F H & Feinleib M (1975) Size of the physiologic cup of the optic ve head *Arch Ophthal (Chicago) 93* 776–780

ooks on quantitative genetics

ner D S (1960) Introduction to Quantitative Genetics Oliver & Boyd Edinburgh and ndon

uson M (1961) Genetics on the Population Level Svenska Bokforlaget Bonniers ckholm

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EFFECTS OF SYSTEMIC AND TOPICAL ADMINISTRATION OF METOPROLOL ON INTRAOCULAR PRESSURE IN HEALTHY SUBJECTS

BY

ALBERT ALM and CARL PETER WICKSTROM

The effect of a single dose metoprolol tablets or eye drops on intraocular pressure (IOP) blood pressure and heart rate was determined in healthy volunteers The ocular tolerance of 6 weeks treatment with 1% eye drops was also studied A 100 mg tablet reduced IOP for at least 10 h with a maximal effect after 4 h corresponding to 32% of the pre-treatment pressure The effects of 25 and 50 mg tablets were less pronounced and of a shorter duration No consistent effect on blood pressure was obtained but doses that reduced IOP also reduced heart rate A short lasting reduction in IOP was obtained with 0 5% eye drops while 1 3 and 5% all caused significant reductions for at least 10-12 h IOP was reduced by 13 20 and [illegible] 4 h after administration of 1 3 and 5% eye drops respectively No effect was observed in the contralateral untreated eye and no cardiovascular effects were obtained after administration of the eye drops 1% eye drops administered twice daily for 6 weeks caused no clinically significant side effect

Key words intraocular pressure – beta adrenergic blockers – metoprolol eye drops – ocular tolerance

During the last 10 years an increasing number of reports have confirmed the observation by Phillips et al (1967) that beta adrenergic blockers reduce intraocular pressure (IOP) Thus significant IOP reductions have been observed for pindolol (Bonomi & Steindler 1975) for propranolol practolol and [illegible] (Wettrell 1977) and for timolol (Zimmerman & Kaufman 1977). Metoprolol, a selective beta 1 antagonist without intrinsic activity and with only weak membrane stabilising properties (Åblad et al 1973) has also been shown to reduce [illegible]

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-matous eyes both when administered systemically (Alm et al 1978) and ly (Ros et al 1978 Krieglstein 1978) The IOP reductions obtained in these were large enough to be of clinical interest Thus the present study was aken to obtain further information on the long term tolerance to metoprolol ops and on dose response relationships for the IOP reducing effect of rolol tablets and eye-drops in healthy subjects

Methods

-ticipants were healthy without any known previous ocular disease The study -ided into three parts

e-response metoprolol tablets

ealthy subjects 8 men and 2 women aged 18–36 years participated in the The study was designed as a randomized double masked single-dose study f the investigators determined IOP by applanation tonometry and the other -c blood pressure (SBP) diastolic blood pressure (DBP) and heart rate (HR) by e clinical methods after at least 5 min rest.

-4 different days with a wash-out time of at least 1 week metoprolol was istered orally as tablets containing 0 25 50 or 100 mg metoprolol at 8 a m 0) IOP was determined at T = −½ 0 ½ 1 and then hourly until T = 10 h as determined in one eye only randomized right or left SBP DBP and HR determined at T = 0 1 2 4 6 8 and 10 h Venous blood for analysis of -rolol was sampled at T = o and 4 h

se-response metoprolol eye drops

-ubjects participating in this study were the same as those that participated in A The study was designed as a randomized double masked single-dose IOP SBP DBP and HR were determined as in study A

4 different days with a wash-out time of at least 72 h metoprolol was -istered as eye drops containing 0 5 1 0 3 0 or 5 0% metoprolol at 8 a m (T One eye only was treated while the other eye received one drop of the vehicle -ion IOP was determined for both eyes at T = −½ 0 ½ 1 2 and then every -d h until T = 12 h SBP DBP and HR were determined at T = 0 and 2 h and -us blood for analysis of metoprolol was sampled at T = 0 and 2 h

cular tolerance to metoprolol eye drops

-healthy subjects all female aged 19 to 42 years participated in the study Each -icipant was furnished with two bottles of eye drops marked right eye and left

eye respectively One of the bottles contained 1% metoprolol in [illegible] while the other bottle only contained vehicle Neither the participant nor the examiner was informed of which bottle that contained the drug The [illegible] applied the eye drops twice daily for 42 days The bottles were [illegible] with fresh solution after 4 weeks

Ocular examination Visual acuity and refraction tear production (Schirmer [illegible]) corneal sensibility (aesthesiometry) and pupil diameter (in a Goldmann [illegible]) were determined before and after 6 weeks treatment with metoprolol [illegible] ocular examination with a slit lamp microscope was performed before and [illegible] weeks treatment and at least twice during the treatment period

Recording of subjective side effects Each participant was requested to [illegible] recordings of possible ocular discomfort Thus the absence or presence of [illegible] itching ocular irritation or visual disturbance should be recorded for each [illegible] following grading system was used

0 = none 1 = slightly but not irritating 2 = marked irritating but unendurable 3 = unendurable

Results

For those participating in the dose response studies the following [illegible] values were obtained IOP 14 3 ± 0 6 mmHg SBP 113 ± 3 mmHg D[illegible] 2mmHg and HR 64 ± 2 (Mean ± SE n = 10)

A Dose response metoprolol tablets

IOP The reduction in IOP observed at various times after administration [illegible] drug was obtained by comparison with IOP at T = 0 IOP at T = -½ did not [illegible] from IOP at T = 0 The results are presented in Table I No effect on IOP [illegible] obtained with placebo while 25 50 and 100 mg tablets all reduced IOP [illegible] effect was obtained 2 5 h after administration of the drug The duration [illegible] magnitude of the effect increased with increasing doses and a significant [illegible] that lasted during all 10 h was observed only for 100 mg At all times of observation the mean reduction obtained with 50 mg was less than the one obtained with [illegible] mg This indicates that a larger dose than 50 mg is required to obtain a [illegible] effect on IOP

HR The reduction in HR was calculated as for IOP The results are presented in Table II Short lasting significant reductions were observed for 25 and 50 [illegible] while 100 mg resulted in a reduction in HR that lasted at least 10 h.

Table I

Reductions in IOP after metoprolol tablets

0 mg			25 mg			50 mg			100 mg		
Mean	SE	P <	Mean	SE	P <	Mean	SE	P <	Mean	SE	P <
−0 8	0 6		0 7	0 6		0 6	0 5		1 7	0 4	0 005
−0 1	0 4		0 1	0 6		1 2	0 4	0 05	2 5	0 8	0 02
0 6	0 7		1 0	0 9		1 6	0 6	0 05	4 2	0 5	0 001
−1 1	0 8		1 3	1 0		2 8	0 6	0 001	3 5	0 7	0 005
−0 9	0 6		2 7	1 0	0 05	2 1	0 8	0 05	4 8	0 7	0 001
0 7	0 7		2 3	1 0	0 05	2 6	0 9	0 02	4 4	1 1	0 005
−0 4	0 6		0 5	0 8		1 8	1 0		4 2	0 5	0 001
0 1	0 7		1 1	0 9		2 3	0 8	0 02	3 6	0 9	0 005
−1 1	0 8		0	0 8		1 9	1 0		3 6	0 9	0 005
1 2	0 8		0 2	0 9		2 1	0 7	0 02	3 5	1 0	0 01
−1 0	0 8		−0 1	0 9		1 3	0 7		2 4	0 4	0 001

d DBP With the differences in SBP and DBP calculated as for IOP and HR ignificant increments and reductions were observed at various times for all including placebo) but no consistent reduction was obtained for either SBP P with any dose

concentration of metoprolol. All pre treatment samples were negative Signifi vels of metoprolol were observed 4 h after administration of 25 50 and 100 blets The obtained serum levels were 71 ± 23 150 ± 47 and 310 ± 85 l respectively No correlation was observed between individual serum ntrations and effect on HR or IOP

Table II

Reductions in heart rate after metoprolol tablets

0 mg			25 mg			50 mg			100 mg		
Mean	SE	P <	Mean	SE	P <	Mean	SE	P <	Mean	SE	P <
3 6	1 2	0 02	9 3	1 6	0 001	7 8	1 6	0 005	9 0	2 1	0 005
−1 4	2 8		5 8	3 0		9 6	2 3	0 005	8 2	3 2	0 05
−2 2	2 3		3 2	2 5		3 6	3 7		6 8	2 3	0 02
−0 6	2 0		0	2 6		−1 0	3 7		4 0	2 6	
−1 8	2 4		0 4	2 3		5 2	3 2		7 8	2 7	0 02
3 6	1 7		4 4	2 3		7 2	2 5	0 02	8 8	3 3	0 025

Table III
Difference (IOP in untreated eyes – IOP in treated eyes) after me[illegible]

Time h	0 5%			1%			3%			[illegible]	
	Mean	SE	P <	Mean	SE	P <	Mean	SE	P <	Mean	[illegible]
0 5	0 1	0 6		1 9	0 4	0 001	1 5	0 4	0 01	[illegible]	[illegible]
1	1 3	0 5	0 05	4 2	0 6	0 001	[illegible] 7	[illegible]	0 01	[illegible]	[illegible]
2	2 0	0 5	0 005	3 0	0 5	0 001	3 [illegible]	0 6	0 001	5 0	[illegible]
4	1 1	0 6		3 0	0 7	0 005	3 4	0 5	0 001	4 1	[illegible]
6	1 4	0 4	0 025	3 0	0 4	0 001	3 3	0 5	0 001	4 0	[illegible]
8	0 6	0 5		2 1	0 6	0 01	2 0	0 6	0 01	[illegible]	[illegible]
10	1 2	0 8		1 5	0 4	0 005	3 0	0 5	0 001	[illegible]	[illegible]
12	0 8	0 6		1 5	0 7		2 7	0 6	0 005	1 9	[illegible]

B Dose response metoprolol eye drops

IOP The effect was calculated as the difference (*IOP in untreated eye* [illegible] treated eye) The results are presented in Table III All doses of metopro[illegible] reduced IOP A significant reduction lasting 10 h was obtained with 1% [illegible] while both 3% and 5% caused reductions that lasted at least 12 h. The ma[illegible] the effect with 5% was numerically larger than that obtained with 1% at a[illegible] observation indicating that 1% may not be sufficient for a maximal effect [illegible] No significant difference in response was observed between 3% and 5% [illegible] No reduction in IOP compared to the pre treatment value was observed [illegible] untreated eye with any concentration of metoprolol used

HR SBP and DBP Reductions were calculated as in the study on the [illegible] tablets No consistent reductions were observed for any parameter with an[illegible]

Serum concentrations of metoprolol None of the concentrations of metoprolol [illegible] the present study caused a significant increase in the measured serum level [illegible] administration of the eye drop

Side effects No side effects were recorded during the two dose-response st[illegible]

C Ocular tolerance study

Subjective side effects The study was initiated as a double-masked st[illegible] participants felt a distinct burning lasting less than 1 min in one of the [illegible] the eye-drops were applied It was always the same eye and when the [illegible] broken it was disclosed that it was the eye that received eye drops conta[illegible]

oprolol None of the participants felt that this moderate transient burning sensation was unacceptable

Apart from this initial burning sensation six participants observed no ocular ... in either eye None of the participants noted any visual disturbance ... four had recorded ocular discomfort graded one or two in one or both eyes ... side effects were mild and transient None of these participants recorded ... itching or irritation for more than 4 days in any eye and for two of them the discomfort was the same in both eyes

... side effects Visual acuity refraction tear production corneal sensibility pupil diameter did not change in either eye during the study Slit lamp examinations of the two eyes were normal before and after the study

In one participant petechial cutaneous haemorrhages appeared on both legs on the third day of the study She had experienced no previous allergic manifestations ... cutaneous haemorrhagies were restricted to that part of the lower legs that was covered by her stockings The participant changed stockings and continued the study The cutaneous haemorrhagies disappeared

Discussion

Effects on IOP HR and BP

Tablets In a previous study 50 mg metoprolol tablets administered three times daily caused a 30% reduction of IOP in eyes with glaucoma (Alm et al 1979) The present study indicates that 50 mg at least as a single dose may be a submaximal ... Whether a single dose of 100 mg is a maximal dose or not cannot be concluded from the present study but the use of larger doses was not considered ... a systemic administration of beta adrenergic blockers to patients with glaucoma would be of clinical interest only if one could obtain a significant IOP reduction at ... levels with a low or moderate effect on the cardiovascular system In the present study 100 mg metoprolol caused a lasting reduction in HR and although the effect of a single dose on the blood pressure at rest is insignificant long term treatment with 100 mg metoprolol tablets can be expected to reduce the blood pressure (Bengtsson 1976)

Eye drops All concentrations of eye drops used in the present study resulted in significant reductions in IOP With an estimated drop size of 50-100 µl a 5% solution would contain 2 5 5 mg metoprolol This dose was not sufficient to cause detectable levels of plasma concentration or measurable cardiovascular effects Still the IOP reduction obtained with 5% eye drops was very similar to that obtained with 100 mg tablets Thus topical or systemical applications seems to be equally

efficient for IOP reductions The mean IOP was reduced by [illegible] respectively 4 h after administration of 3% 5% eye drops and [illegible] respectively This is similar to the reductions of IOP in healthy volunteers [illegible] with other beta adrenergic blockers Reductions between 20% and [illegible] reported for timolol eye drops (Katz et al 1976) [illegible] injections of [illegible] oxprenolol (Sharaf et al 1974) and oral administration of propranolol [illegible] and atenolol (Wettrell & Pandolfi 1975) Since these various beta [illegible] blockers differ regarding degree of selectively for beta 1 and beta 2 [illegible] intrinsic activity and membrane stabilising properties it seems clear [illegible] properties play a minor role in determining the effect on IOP It has [illegible] been discussed that a mechanism other than a beta adrenergic blockade [illegible] responsible for the reduction in IOP (Neufeld 1979)

Ocular tolerance

In the present study 1% metoprolol eye drops given twice daily for [illegible] result in any unacceptable ocular side effect However Van Joost et al (1979) [illegible] reported a high incidence of conjunctival oedema and hyperaemia and [illegible] dermatitis in patients treated with 1-4% metoprolol eye drops Thus 11 of [illegible] patients experienced adverse reactions two weeks to five months after [illegible] treatment and in 5 of these 11 patients a positive patch test indicated that [illegible] have been caused by a delayed type of hypersensitivity The reason for [illegible] discrepancy between these results and the results of the present study [illegible] The duration of treatment may be important In the study of Van Joost et al [illegible] only four patients experienced adverse reactions within six weeks, the [illegible] the present study

In summary the results of the present study indicate that metoprolol [illegible] may be useful in the treatment of glaucoma 1 3% eye drops administered [illegible] daily seems to be an adequate dose schedule However long term studies [illegible] effect on IOP and the incidence of side-effects are needed before the [illegible] usefulness can be evaluated

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References

B Carlsson B & Ek L (1973) Pharmacological studies of two new cardio-selective nergic beta receptor antagonists *Life Sci 12 part I* 107–119

L Wickstrom C P Ekstrom C & Öhman L (1979) The effect of metoprolol on aocular pressure in glaucoma A pilot study *Acta ophthal (Kbh) 57* 236–242

— sson C (1976) The effect of metoprolol – a new selective adrenergic beta₁ receptor king agent – in mild hypertension *Acta med scand 199* 65–70

m L & Steindler P (1975) Effect of pindolol on intraocular pressure *Brit J Ophthal* 301–303

M, Hubbard W A Getson A J & Gould A L (1976) Intraocular pressure decrease ormal volunteers following timolol ophthalmic solution *Inve t Ophthal 15* 489–492

lstein G K (1978) Die Wirkung von Metoprololtartrat auf den Augendruck *Klin Mbl enheilk 173* 632–637

ld A H (1979) Experimental studies on the mechanism of action of timolol *Surv thal 23* 363–370

ps C I Howitt G & Rowlands D J (1967) Propranolol as ocular hypotensive agent *t J Ophthal 51* 222–226

E Dake C L Nagelkerke N J D & Greve E L (1978) Metoprolol eye drops in the atment of glaucoma A double blind single-dose trial of a beta₁ adrenergic blocking ag *Albrecht v Graefes Arch klin exp Ophthal 206* 247–254

if E Hauron E A Ishaac Z Shewy T M E & Nassef A E H (1974) The effect of ne beta adrenergic blockers on human intraocular pressure *Exp Eye Res 19* 923–925

Joost T Middelkamp Hup J & Ros F E (1979) Dermatitis as a side-effect of longterm ical treatment with certain beta blocking agents *Brit J Dermatol 101* 171–176

rell K (1977) Beta adrenoceptor antagonism and intraocular pressure A clinical study propranolol practolol and atenolol *Acta ophthal (Kbh)* Suppl 134

rell K & Pandolfi H (1975) Effect of oral administration of various beta blocking agents the intraocular pressure in healthy volunteers *Exp Eye Res 21* 451–456

merman T J & Kaufman H E (1977) Timolol A beta adrenergic blocking agent for the atment of glaucoma *Arch Ophthal (Chicago) 95* 601 604

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REFRACTIVE CHANGE IN ALLOXAN DIABETIC RABBITS CONTROL BY FLAVONOIDS I

BY

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The rabbit eye is hyperopic by approximately 4D The induction of diabetes leads to a further enhancement in the degree of hyperopia. This enhancement is attenuated substantially by flavonoids as inhibitors of aldose reductase. The development of refractive changes in diabetic lens involves aldose reductase catalyzed polyol synthesis

Key words diabetes – cataracts – refractive change – bioflavonoids – aldose reductase and polyols

The occurrence of cataracts in certain diabetic strains of animals is well known (Yerganian & Meier 1959 Schmidt Nielson et al 1967 Hacket et al [illegible] et al 1968) The formation of cataracts in these strains and in experimentally diabetic animals is preceeded by an accumulation of excessive sorbitol in the lens [illegible] Heyningen 1959) This lenticular accumulation of sorbitol is a consequence of the action of the tissue aldose reductase on excessive glucose available in diabetes (Glucose + NADPH + H^+ $\xrightarrow{\text{aldose reductase}}$ sorbitol + NADP) A portion of sorbitol gets oxidized to the ketosugar fructose (Sorbitol + NAD $\xrightarrow[\text{dehydrogenase}]{\text{sorbitol}}$ fructose + NADH + H^+) Thus the lenses of diabetic animals also contain elevated levels of fructose (Kinsey et al 1959 Kuck 1961) An accumulation of the excessive sorbitol and fructose in the lens fibers and epithelium has been proposed to induce osmotic swelling of the tissue and its ultimate opacification (Kinoshita et al 1962, [illegible] Chylak et al 1969) Cataract in diabetes is in fact a consequence of aldose reductase catalyzed polyol synthesis and its accumulation has been demonstrated

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nongly by recent in vivo experiments Treatment of experimentally diabetic ils with certain flavonoids a class of compounds inhibitory to aldose reductase na et al 1975 1976) leads to a delay of cataractogenesis (Varma et al 1977 Juliani et al 1979) This delay by flavonoids is accompanied by a decrease in ular sorbitol and fructose *It is more difficult to implicate lenticular sorbitol* synthesis is incumbent upon the activity of aldose reductase in concert with relevant aspects of tissue metabolism (Van Heyningen 1969 1976 Kuck Varma & Kinoshita 1974a b) in the formation of cataracts in human tes The degree of hyperglycemia and ketoacidosis duration of the disease he age at its onset dietary factors such as proteins and vitamins environmental rs such as light and genetic traits are some other possible variables affecting the e of cataractogenesis In addition there is considerable variation in levels of tol and fructose in human lens (Pirie & Van Heyningen 1964 Heaf & Galton Varma et al 1979) The levels attained are however proportionate to blood se concentration (Varma et al 1979) A precise evaluation of the role of aldose ctase and polyol accumulation in the development of opacity by in vivo use of itors of aldose reductase in human diabetics has not been practical

 early effect of diabetes in man consists of refractive changes This was first ned by *Horner in 1873 (Ref Waite & Beetham 1935) The refractive changes* be myopic (Duke Elder 1925 Gwinup & Villarreal 1976) as well as hyperopic rsman 1973) and are primarily because of lens changes (Fleshing 1923 Vere & el 1954) Whether this manifestation of refractive error is linked with aldose ictase activity is not known although it is presumed that these refractive changes ct the initial steps of cataractogenesis The purpose of this investigation was to ascertain this possibility using rabbits as experimental models These studies form the basis of further studies on control of ocular refraction in human etics by aldose reductase inhibitors and possibly ultimate prevention of cataracts ich individuals through inhibitors of aldose reductase

Materials and Methods

no rabbits weighing 800 ± 200 g were used as experimental animals All nals were without any obvious ophthalmologic lesions Diabetes was induced by avenous administration of alloxan monohydrate (5% aqueous) in the dose of 10 100 g weight of the animal Animals were fasted for 48 h prior to receiving xan Administration of the latter was done under light anesthesia imposed by ed inhalation of diethyl ether vapor Immediately after alloxan administration animals received 20 ml of 10% glucose solution intraperitoneally This was owed by two further glucose injections one after 4 h and the other after 24 h of

the alloxan administration Drinking water consisted of a 5% glucose solution [illegible] 48 h The method was essentially similar to that used by Reddy & Kinoshita [illegible]

Refractive state of the eye was monitored by streak retinoscopy under [illegible] cyclopegia The cyclopegic used was 1% atropine sulphate drops [illegible] times in the morning in the conjunctival cul de sac at intervals of [illegible] retinoscopy was performed 1 h (enough for full cyclopegia) after the [illegible] instillation of atropine drops Baseline refractive power was ascertained by [illegible] copy on five successive days The readings on the latter three days were [illegible] within 0 5 D and hence provided reliable control data The meridian [illegible] value was taken for calculation The trend of the results was unaffected [illegible] meridia with lower values were considered Animals restrained in a [illegible] when hand held were fully cooperative The distance between the person doing [illegible] refraction and rabbit was 75 cm

Table I
Material and treatment

Group of Animals	Number of Animals	Treatment
1 Normal control (I)	6	no treatment
2 Diabetic control (II)	6	placebo started 3 days before alloxan administration and continued throughout the experimental period
3 Diabetic prophylactic (III)	6	flavonoids started 3 days before [illegible] of alloxan
4 Diabetic early (IV)	6	flavonoids started 1 week after [illegible] of alloxan
4 Diabetic early (V)	6	flavonoids started [illegible] weeks after [illegible] of alloxan
4 Diabetic early (VI)	6	flavonoids started 3 weeks after [illegible] of alloxan

The bioflavonoids quercetin and quercitrin (Varma et al 1975) were used as aldose reductase inhibitors Quercitrin was used in a 5% solution made in 1% cystein HCl adjusted to pH between 8 0 to 8 4 The solution was maintained sterile by millipore filtration antibiotics (pencillin 100 units/ml streptomycin 100 mg/ml) and antimycotic (amphotericin B 0 25 µg/ml) Quercetin was used as 5% suspension in 5% aqueous glycerol The inhibitors were administered in a dose of 0 34 mg/g animal weight divided between subconjunctival intraperitoneal and oral routes The subconjunctival daily dose was 0 5 ml in each eye of quercitrin solution (25 mg/eye) The intraperitoneal dose consisted of 2 ml of the glycerol suspension of quercetin (100 mg/animal) The oral dose was 150 mg/day/animal derived from administration of the 5% aqueous quercetin suspension Quercitrin the more potent of the two flavonoids with regard to its aldose reductase inhibitory activity is scarcely available and hence its use was limited for subconjunctival route only

The placebos consisted of 1% cystein HCl (adjusted between pH 8 to 8 4) and 5% aqueous glycerol both fortified with antibiotics and antimycotic as described above No placebo was used for aqueous quercetin administered orally (3 ml) Animals were classified and treated according to the protocol given above (Table I) and retinoscoped for 12 weeks After this period the lenses were cloudy for accurate refraction

The animals were ascertained to be normoglycemic before administration of alloxan Diabetes was evidenced by elevation of the blood sugar level to a minimum of 300 mg/100 ml after 72 h of alloxan injection the average level Being 400 ± 100 mg/100 ml The determination of blood sugar was done on samples obtained from ear veins and using the enzymatic method involving glucose oxide and glucose peroxidase reaction (Keston 1956) All diabetic animals were checked for the level of hyperglycemia at weekly intervals

Results

The powers of lenses (diopters) required to neutralize the refractive errors in normal and diabetic control rabbits at various experimental stages have been depicted graphically in Fig 1 In the group of normal animals the power of the lens required to neutralize the refractive error was approximately 4 0 ± 0 5 D the refraction in the early part of the experiment being slightly on the lower side Fasting for periods up to 48 h was also observed to lower the refraction by 0 5 ± 0 25 D Therefore the animals were retinoscoped routinely in an unfasted state The contralateral eye of the same animal differed by < 1 D Anisometropia exceeding 4 D was rare

Rendering the animals diabetic by alloxan lead to significant changes in ocular refraction From an average of + 4D recorded before the onset of diabetes the

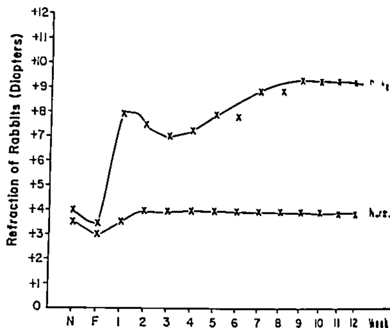


Fig 1

Effect of diabetes on ocular refraction Normal Each point represents an avera
The period of fasting (F) was 24 h ↘ = nonfasted animals The number of animals
in diabetic group was similar to that in the group of normal animals. The bl
diabetic groups was 400 ± 100 mg%

refraction rose rapidly to an average of + 8 0 ± 0 1 D by the end of the first
after alloxan administration This deviation was followed by a small dep
commencing between the 1st and 2nd week and ending at the 5th wee
minima being at the 3rd week Following the fifth week there was a secon
This rise was however more gradual than the initial one and led
subsequently to a plateau 9 ± 1 0 D The refraction at the plateau was thu
greater than the initial peak observed at the end of the first week (8 D) The
in the refractive status was thus clearly biphasic though the most p
change occurred in the first phase coincident with the initial establish
diabetes Elevation coincident with periods in the second phase in compar
that in the first phase was rather small (1 to 2 5 D) but consistent. Transie
vacuoles were also observed during the experimental periods. One of the
eyes in the diabetic control group had a vitreal haemorrhage The re
changes reported herein were observed consistently including those in thre
experiments each pilot experiment being done on eleven diabetic rabbits. I
also true in cats and dogs However it was difficult to render cats diabet
were inconvenient to use in these long term experiments.

[illegible]													
I	0	0 (0.24)	0.5 (0.25)	0.5 (0.36)	0.5 (0.39)	0.5 (0.31)	0.5 (0.34)	0.5 (0.42)	0.5 (0.34)	0.5 (0.25)	0.5 (0.10)	0.5 (0.40)	0.5 (0.39)
II	0	4.0 (1.20)	3.5 (0.22)	3.0 (1.19)	3.25 (1.33)	4.0 (1.62)	4.0 (1.69)	5.0 (1.91)	5.0 ([illegible]30)	5.5 ([illegible]68)	5.[illegible] (1.79)	5.5 (0.47)	5.5 (0.62)
III	0	1.5 (0.94)	2.0 (0.19)	1.0 (0.65)	1.5 (0.5)	1.5 (0.35)	0.5 (0.35)	0.5 (0.2[illegible])	0.5 (0.21)	0.5 (0.22)	0.5 (0.35)	0.5 (0.[illegible]8)	0.5 (0.31)
IV	0	4.0 (0.63)	[illegible].0 (0.6[illegible])	2.0 (0.80)	1.75 (0.71)	1.5 (0.99)	1.0 (0.37)	1.0 (0.37)	1.0 (0.36)	2.0 (0.50)	2.[illegible] (0.1[illegible])	2.5 (0.4[illegible])	2.5 (0.53)
V	0	3.5 (0.[illegible]6)	4.0 (0.06)	3.0 (0.0[illegible])	3.0 (0.54)	3.0 (0.17)	3.0 (0.88)	2.5 (0.59)	[illegible]5 (0.81)	3.5 (0.[illegible])	4.0 (0.93)	4.5 (0.55)	4.5 (0.44)
VI	0	3.[illegible] (0.75)	3.0 (0.[illegible]9)	[illegible] (0.18)	3.0 (0.00)	3.0 (0.93)	2.0 (1.3[illegible])	[illegible] (1.93)	3.0 (1.[illegible])	3 (1.69)	4.0 (1.64)	4.5 (1.30)	4.5 (1.0[illegible])

I Normal control

II Diabetic control received placebos starting 3 days before alloxan injection

III Diabetics receiving flavonoids starting 3 days prior to alloxan treatment

IV Diabetics given flavonoids 1 week after alloxan treatment

V Diabetics given flavonoids 2 weeks after alloxan treatment

VI Diabetics given flavonoids 4 weeks after alloxan treatment

The doses of flavonoids have been given in the text The bolld sugar of all diabetic animals was 400 ± mg

The differences at various stages between the initial refraction and that prevalent after treatment in different groups of rabbits abbreviated as Δ D are described in Table II Fig 2 represents the graphic trend of such dioptric changes In normal controls (Group I of Table II) it varied between 0 and 0.5 Fig values in diabetic control (Group II of Table II) is represented by Le II d Fig At intervals of 1 2 3 4 6 8 10 and 12 weeks the Δ Ds were 4 3 5 3 5 5 5 5 and 5 5 D respectively As would be apparent from the graph and as found earlier (Fig 1) this increase in hyperopia appears to level off after six weeks establishment of diabetes

The trend of changes in the diopteric power of the eyes in rabbits treated flavonoids as summarized in Fig 2 and Table II indicates that this treatment minimizes the effect of diabetes on the refractive power the effect being pronounced in groups given flavonoids either before the onset of diabetes or after

Discussion

The results described in the preceeding sections demonstrate that the rabbit like that of many other terrestrial animals (Duke Elder 1958) is hyperopic compared to the human eye The extent of hyperopia in the present investigations was approximately 4D However the value was somewhat

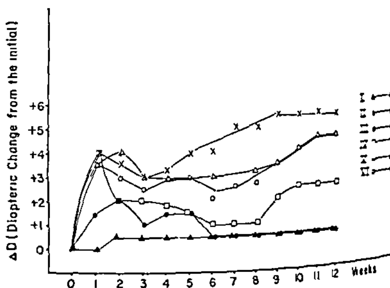


Fig 2

The numbers indicate the difference in refraction at a particular stage from the refraction at 0 day Each group consisted of six animals. The figures represent the of 12 days The group designations are same as in Table I

TABLE III

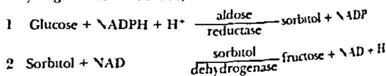
Statistical analysis of the data in Table II (t values). If degree of freedom ... t ... 8 = P < 10⁻³ is considered to indicate significant difference between the groups compared

Groups Compared	1		3	1		6	7	8	9	10	11	12
I X II	11 23	31 8	6 94	7 0	7 32	7 0	7 96	1 71	1 13	9 1	27 77	23 82
I X III	3 57	16 8	2 38	5 88	7 11	0	0	0	0	0	0	0
I X IV	17 01	7 50	1 00	5	3 33	3 11	3 13	3 52	9 37	15 71	11 76	19 52
I X V	17 01	17 70	1 31	13 81	11 70	1 15	1 52	9 1	17 11	12 96	21 00	3 52
I X VI	13 01	13 58	11 76	11 71	8 77	3 7	3 38	10	6 12	7 36	10 21	12 92
II X III	5 18	17 8	5 12	1 27	5 20	7 0	8 18	1 77	6 1	9 1	31 2	2 02
II X IV	0	7 6	10	3 18	1	1 0	7 11	5 9	8 8	1 3	16 1	13 02
II X V	1 31	2 1	0	0 10	01	1 8	1 33	3 1	1 10	2 51	1 76	1 2
II X VI	1	2 71	1 3	0 8	1 8	3	3 13	2 11	1 61	1 12	1 2	2 12

lower side of the mean (by < 0 5D) in the first week of the experiment b; beginning of the second week the refraction was steady and stayed over mean The slight increase in refraction noticed towards the end of the week may be due to the growth of the animals or their adaptation to the conditions A combination of the two could also be operative These changes in normal rabbits are however much smaller in comparison to the diabetic animals

Figures presented in Table II indicate that induction of diabetes led to a enhancement of the extent of hyperopia the A D (dioptric difference from initial value at 0 day) being approximately 4 diopters at the end of the first after alloxan administration (Group II) This change is far greater as compared that in the normal control group (I) A reference to Table III wherein the been quantitatively analyzed would indicate that the t values between groups were highly significant ($t = P < 10^{-5}$) at all points of examination The results thus clear in demonstrating that a refractive change is in the hyperopic direction and is one of the characteristic and predominant manifestations of the syndrome This was in conformity with exploratory experiments conducted three wild pigmented rabbits six dogs and four cats Thus, the albino rabbit considered convenient for the present detailed ophthalmological studies the period of examination diabetes inflicted hyperopia once established, rather narrowly (Fig 1) so much so that finally the refraction was observed follow a platau covering a range of 1 2 diopters with a median value of 9 D consistency in the range of variation is in keeping with the range over which weight of the animals and their blood glucose varied The blood glucose of diabetic animals varied within 200 mg per cent (mean 400 ± 100 mg) The weight of the animals varied by not more than 200 g

The geometric and the physico-chemical factors which might lead to the above refractive changes in diabetic animals are not well understood at the present and further studies are needed in this direction However since the treatment of diabetic animals by flavonoids decreases accumulation of sorbitol and fructose in the lens (Varma et al 1977 1978 1979) excessive refractive changes observed in diabetic animals not given flavonoids (Group II) in comparison to that in animals given flavonoids (Group III) suggest that development of hyperopia in diabetes may be a consequence of excessive synthesis of sorbitol and fructose. The above polyol and the ketosugar are synthesized by the following two reactions Heyningen 1959 Kuck 1961)



1 Glucose + NADPH + H⁺ $\xrightarrow[\text{reductase}]{\text{aldose}}$ sorbitol + NADP

2 Sorbitol + NAD $\xrightarrow[\text{dehydrogenase}]{\text{sorbitol}}$ fructose + NAD + H

aldose reductase is the first enzyme in the above series and its activity is .ed by flavonoids (Varma et al 1975) it appears that this enzyme participates iating refractive changes just as it does to initiate cataractogenesis The tive change thus may be an essential event linked with the genesis of lens y in experimental diabetes A comparison (Table III) of refractive changes :cur in control diabetic animals (Group II) and that in diabetic animals treated lavonoids (Group III) indicates that the attenuation of refraction by flavonoids . diabetic animals (Group III) is quite substantial and remains highly icant throughout the experimental period (*t* is always ≥ 10 $P < 10^{-3}$) The opic peak attained after 1 week of diabetes in the latter animals (Group III) is 0% of that in the control diabetic animals (Group II) treated with placebo In quent periods the refraction in Group III almost normalized though they all ained a *consistent hyperglycemia equivalent to that in the control diabetic* ils The findings also suggest that the hyperopia is not necessarily linked with a ing of blood sugar as often contended (Duke Elder 1925)

'atment of animals (Group IV) when started at the peak of hyperopia ring one week after the onset of diabetes also led to a significant return ds the baseline refraction (Group I) Following one week of such treatment :tion in diabetic Group IV fell down to half of that existent before treatment was followed by a further decline towards normal till at the end it stayed close proximately half of that in the diabetic control (Group III)

hough commencement of treatment at periods 2nd (Group V) and 3rd week ıp VI) after the onset of diabetes also resulted in a lowering of hyperopia this ase was much less striking as compared to that in Groups III & IV where nent was *started either 3 days prior to the administration of alloxan (III) or 1* after alloxan administration (IV) Thus an earlier treatment leads to a better nosis In addition these observations are in conformity with the earlier reports ing reversibility of galactose cataracts in rats if the galactose from the diet is ved well before the advanced stages of cataracts have reached

ie salient difference between these animal studies and the human reports sts of the type of refractive error In human diabetes such an error can be rds hyperopia as well as myopia (Bellows 1935) although literature suggests myopia is more common Further studies are therefore in progress to relate oolvol induced changes such as hydration and the concomitant alterations in ietric parameters of the lens in reference to its converging power The effect of etes will obviously be algebric to the physico-chemical and biometric events A iioco-chemical *effect may consist of dilution of the lens constituents resulting in* l of the refractive index the dilution being due to sorbitol induced hydration ·fall in refractive index is likely to be compensated by an increase in refraction use of geometric alteration consequent to swelling If the geometric alteration

is low hyperopia will predominate On the other hand if ... the fall in refractive index because of dilution the result can be ... heterogenity of the lens segmental nature of its hydration in ... variation in its elasticity with age are other complications These ... are currently being studied in this laboratory Nevertheless the ... indicate that the initial event in altering the refractive index of ... consequent biometric change may involve aldose reductase and ... likely by the use of pharmacological agent such as flavonoids and other ... this enzyme The susceptibility of human lens polyol accumulation ... reductase has been previously demonstrated (Chylak et al 19 9 Varma 1979)

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References

Bellows J G (1944) The crystalline lens in diabetes mellitus *Arch Ophthal* ... 498–507

Chylack L T Jr & Kinoshita J H (1969) A biochemical evaluation of cataract ... high glucose medium *Invest Ophthal* 8 401–41...

Chylack L T Henriques H F & Tung W H (19 9) Inhibition of sorbitol ... human lens by an aldose reductase inhibitor *Docum ophthal* 8 6...– 3

Duke Elder S (1925) Changes in refraction in diabetes mellitus *Brit J Ophthal* ...

Duke Elder (1958) System of Ophthalmology Vol I p 639 C V Mosby Co

Eversman J (1971) Comprehensive approach to diabetes mellitus ... 23

Fisching A (1923) Refraktionsanderungen bei diabetes mellitus *Med Klin* ...

Gwinup G & Villarrela A (1976) Relationship of screen glucose concentration to refraction *Diabetes* 25 29–31

Hackel D B Mikat E Lebovitz H E Schmidt Nielson D Horton E S & ... (1967) The sandrat as an experimental model in studies in diabetes mellitus ... 130–133

Heaf D J & Calton D J (1975) Sorbitol and other polyols in lens adipose tissue and diabetes mellitus *Clin Chem Acta* 63 41–47

Juliani H R Pohl M G Richards R D and Varma S D (19 9) Aldose reductase ... *Invest Ophthal & Vis Sci* 15 Supplem ... 212

Keston A S (1956) Specific colorimetric enzymatic reagents for glucose ... 129th Meeting A C S p 310

Kinoshita J Merola L Satoh K & Dikmak E (19...) Osmotic changes caused ... accumulation of dulcitol in lenses of rats fed with galactose *Nature* ...

ta J H (19 4) Mechan sms ın tıatıng cataract formatıon *In v t Ophthal. 13* 713 794
V E Watchl C Kuck J F Jr & Reddy D V (19ɔ8) *Current research on culture n*
-s Concıll um Ophthal Belgıca 17 86ɔ 8 9
J F (1961) The formatıon of fructose n ocular lens *Ar h Ophthal. (Chıcago) 65*
846
J R (1966) Sorb tol pathway metabol es ın the d abetıc rabb t lens *In v t Ophthal 5*
4
L & Van Heyn ngen R (1964) The effect of d abetes on the content of sorb tol glucose
tose and nos tol n the human lens *Exp Eye Res 3* 124 131
D V & Kinsey V E (1963) Transport of am no acıds nto ntro-ocular flu ds and lens
ıabetıc abb ts *In v t Oph hal. 2* 237–242
d Nelson K Ha ns H B & Hackel D B (1964) Dıabe es mell tus n the sandrat
u ed by standard laboratory d ets *Sc ence 143* 689–690
Heyn ngen R (19ɔ9) Formatıon of polyols n the lens of ra w th sugar cataract. *Na u e*
194 19ɔ
Heyn ngen R (1969) The Lens Metabol sm and cataract n the e e 2nd Ed pp
400 431 444 (Ed) Davson H New York Academ c Press
Heyn ngen R (19 6) Sugar alcohols n the pa hogenes s of galactose and dıabetıc
aracts *B rth Defe ts 12* 29ɔ–303
ıa S D & Kınosh ta J H (1974) The absence of cataracts n m ce wı h congen tal
e gl cemıa. *Exp E e Res 19* 577 ɔ82
a S D & K nosh ta J H (1974) Sorb ol pathway n d abetıc and galactosem c ra lens
ch m B phys A ta 338 632 640
ıa S D M kunı L & Kınosh ta J H (1975) Fla ono ds as nh b ors of lens aldose
luctase *Scıen e 188* 121ɔ–1216
ıa S D & Kınosh ta J H (19 6) Inh b tıon of lens aldose reductase by fla ono ds The r
ssıble role n the p e en on of dıabet c cataracts *Bıochem Pharmacol 25* 2ɔ0ɔ 2ɔ13
na S D Mızuno A & K nosh ta J H (1977) Dıabetıc cataracts and fla ono ds *Scıence*
5 0ɔ 206
na S D (19 8) Delay ng the format on of cataracts n d abetes Proceedıngs of the Inter
ngress of Eye Research Osaka Japan III p 113
na S D Schocket S S & Rıchards R D (1979) Impl catıons of aldose reductase n
taracts n human dıabetes *In e t Ophthal & V ıs Scı 18* 237 241
D W & Verrel D (19ɔɔ) Relatıon between blood sugar le el and the optıcal propertıes
the lens of the human eye *Cl n Sc 14* 183–196
te J H & Betham W P (1935) The v sual mechanısm n d abetes mell tus *Neu E g J*
d 212 367 3 9 429 443
P H We r B J H me J H & Forrest E (1968) Impl catıons of hyperglycemıa and
taract n a colony of tuco tucos (ctenomystalarum) *Natu e 219* 1374 13 6
gaman G & Me er (19ɔ9) Spontaneous hered tary dıabetes mellıtus ın the Ch nese
ms er *F d P oc 18* 5ɔ4

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ON THE OPTICAL MEASUREMENT OF CORNEAL THICKNESS

I Optical Principle and Sources of Error

BY

THOMAS OLSEN CARSTEN BO NIELSEN and NIELS EHLERS

The optical principle for the estimation of corneal thickness with a commonly employed method is considered The theoretical relationship between the apparent and true corneal thickness is described in a simple manner Based on the theoretical results it could be confirmed that physiological variations in refractive index and radius of the cornea induce an insignificant error in the corneal thickness estimate The theoretical relationship between apparent and true corneal thickness was compared to the performance of two commercially available pachometers (Haag Streit and Zeiss) The actual reading of the pachometers was found to be lower than the theoretical reading by a non linear error amounting to about 0 010 and 0 100 mm at a true corneal thickness of 0 50 and 1 00 mm respectively

Key words corneal thickness – pachometer – optical principle

Several methods have in the past been proposed for the optical measurement of corneal thickness (Ehlers & Kruse Hansen 1970) Today one of the most widely used methods is based on the optical principle originally described by Jaeger for the measurement of chamber depth The optical principle worked however for the measurement of corneal thickness also

The increasing use of corneal thickness determination in ophthalmology practice places an increasing demand on the accuracy and reproducibility of the method From a theoretical point of view the optical properties of the cornea makes it almost a perfect organ for optical measurements. However the basic values reported by different investigators still differ considerably The advantage of as much standardization as possible in this field is therefore evident.

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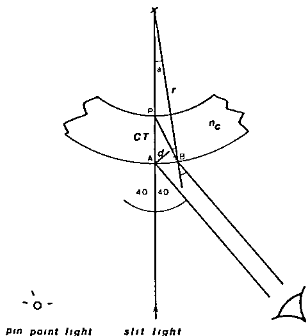


Fig 1

[…]al situation for the estimation of corneal thickness when the optical section is viewed at a […] angle (= 40°) and the slit light is perpendicular to the corneal surface The apparent […]ness (d) depends on the true corneal thickness (CT) refractive index of the cornea (n) and the radius of the anterior surface of the cornea (r)

[…] the present paper the optical principle of the corneal thickness determination […]nodum Jaeger is given a reconsideration Based on the theoretical results the […]cal performance of two commercially available pachometers that of the […]g Streit and the Zeiss 30 SL slitlamp are evaluated

[…]ical situation (Fig 1)

[…]orrect measuring situation requires that the slit light falls perpendicular to the […]neal surface This can be approximated by asking the subject to look directly into […] slit light source Secondly the optical section must be observed at a known and […]d angle (= 40 in the commercially available pachometers) The geometry of the […]uation can be stabilized very much if two vertically mounted pin point lights are […]ced at the one side of the incident slit beam so that they can be reflected at the […]face of the cornea at an angle which equals the observation angle and viewed […]ough the eyepiece (Mishima & Hedbys 1968 Ehlers & Sperling 1977)

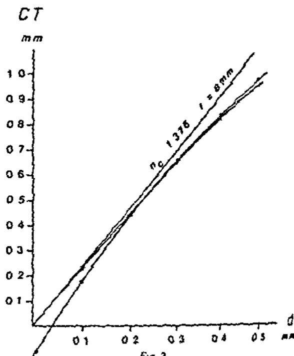


Fig 2

The theoretical relationship between apparent (d) and true corneal thickness (CT) for a standard cornea of n = 1 376 and r = 8 mm (upper curve) The two lower curves represent the reading of two commercially available pachometers Haag Streit (curve with ... Zeiss (curve with black dots)

The procedure is to measure the apparent thickness of the optical section observed at a fixed angle and transform this value into a true corneal thickness. This is done in one step with the commercially available pachometers where the reading allows a direct reading of the thickness from the angular displacement of the beam splitter

The apparent thickness (d) is a function of the true thickness (CT) the refractive index (n_c) and the anterior radius (r) of the cornea The exact function (at a fixed observation angle) which defines CT as a function of d

CT = f(d) for given values of r and n_c

is however not easily calculated In the following a simple empirical ... given

We assume an extremely narrow slit

With a fixed observation angle (= 40) the posterior limit of the optical section ... through a point B at the surface of the cornea A denotes the anterior ... section We now introduce a the angle of cornea corresponding to AB For given r and n both the apparent (d) and the true thickness (CT) of the cornea can now be expressed in terms of a

s a function of a

$$d = |AB| \times \cos(\angle dAB)$$
$$= 2 \times r \times \sin(\tfrac{1}{2}a) \times \cos(\angle dAB)$$
$$= 2 \times r \times \sin(\tfrac{1}{2}a) \times \cos(40^\circ - \tfrac{1}{2}a) \quad (2)$$

as a function of a

e have

$$\frac{\sin(i)}{\sin(u)} = n$$

$$i = 40 - a,$$

which u can be found

idering triangle APB we have

$$\angle APB = u + a \text{ and}$$
$$\angle ABP \quad 90^\circ - \tfrac{1}{2}a - u$$

ine relations now give

$$\frac{|AP|}{\sin(\angle ABP)} = \frac{|AB|}{\sin(\angle APB)}$$

$$|AP| - CT \quad \frac{2 \times r \times \sin(\tfrac{1}{2}a) \times \sin(90^\circ - \tfrac{1}{2}a - u)}{\sin(u + a)} \quad (3)$$

graph of (1) can now be constructed by calculating d and CT for a number of different r given values of r and n This can be done by hand but is easily done with the assistance programmable desk calculator (see appendix)

theoretical pachometer reading

2 shows the calculated relation between apparent and true thickness for a dard cornea (r = 8 0 mm n_c = 1 376) Also included is the performance of the g Streit and Zeiss pachometer The latter curves were made by measuring an xt micrometer (Leitz) perpendicular to the pachometer in question with the ro-scale divided optically in two halves by the beam splitter One half of the ge was then displaced corresponding to 0 005 0 10 0 15 mm etc on the rometer and the corresponding scale reading of the pachometer recorded for h setting The pachometer readings are seen to be lower than the theoretical ost linear curve especially for higher values At 0 5 mm of corneal thickness the hometer curves were about 0 01 mm below At 1 0 mm the difference was about 00 mm The readings of the Haag Streit and the Zeiss pachometer were very ilar except for small values where the curve from the Zeiss pachometer differed re from the theoretical curve and intercepted the ordinate at a negative value

Fig 3 shows in a larger scale the effect of varying anterior radius and refractive lex of the cornea The error of varying the radius amounts to about 1% when the dius is changed from 8 down to 6 or up to 12 mm It can be calculated that the dius should be less than 4 mm to induce an error of 5% or more an error which ould never be reached for values above 8 mm

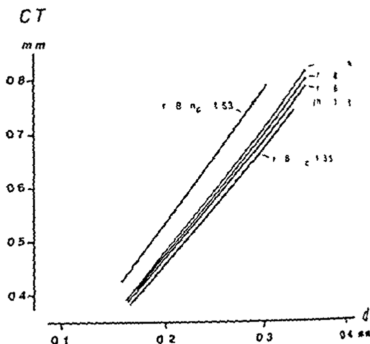


Fig 3
Theoretical relationship between apparent (d) and true thickness (CT) of cornea for values of refractive index (n) and radius of anterior surface r)

The refractive index of the living cornea is not likely to change very much. The most important direction of change is towards lower refractive index when the cornea imbibes water. If the cornea was pure aqueous humour (refractive index 1.336) the error on the corneal thickness determination would be about 4% (lower curve in Fig 3). This error is of course never reached. If the cornea would double thickness by intake of aqueous humour the resulting refractive index would be expected to be approximately 1.356 (mean value between the normal value and that of aqueous humour). The resulting error on the thickness determination is only 2%. Upper curve in Fig 3 is the theoretical curve for a cornea made of ... (refractive index 1.525)

Comments

The theoretical outline of the optical conditions given in the present work shows that the corneal thickness measurements are only insignificantly influenced by variations in refractive index and radius of the cornea. Of these factors

d cornea (anterior rad us less than 4 mm) would induce an error of more than

optical performance of t o commercially available pachometers were found ia e slightly from the theoretical s tuation by a non l near error wh ch was est at h gh corneal th ckness The non l near error sho n in the present study e Haag Stre t pachometer were in good aggreement (within 0 01 mm) with rrection values given by this firm n a correction table A s m lar table is not ble for the Zeiss pachometer

s puzzling hy the pachometer of the latter f rm has been constructed so that o corneal th ckness a negative read ng was obtained

e non linearity of the pachometer curves is the result of the l near scale of the meters h ch corresponds to an angular displacement of the two plane lel plates of the beamspl tters From a practical point of vie v this scale ndent error seems unfortunate Looking up a correction value in a table each a reading is taken is a cumbersome procedure For normal corneal th cknesses nd 0 5 mm the error s of course of minor mportance but when correct lates of changes n corneal th ckness abo e this alue are wanted a correction is ssary It may be suggested that f the construction of the beamsplitter is not to te ed and a greater reading accuracy is des rable a s mple techn cal mpro e- t may be to change the linear scale into a slightly non linear scale wh ch has calibra ed with the theoretical curve dep cted n F g 9

e practical problems concerned with the optical measurement of corneal ness will be dealt with in a following paper

Appendix

d on equations (2) and (3) this p ogram calcula es correspond ng alues of d and CT n en alues of and n by s epwise ncreas ng the alue of a until the alue of CT eds 1 mm In othe wo ds the program calcula es a number of po nts on the graph of CT d fo any gi en alue of r and n

gramm ble calcula or HP 97

outine B S o es the alue of r (n mm)

outine C S o es the alue of n

routine D S o es the value (n degrees) by wh ch a s wan ed o increase for each pair of d and CT

r tine A n tializes the p ogram

LB STO1 RTN LBLC STO9 RTN LBLD STO6 RTN LBLA DEG RCL1 PRTX/RCL2 N SPC SPC 0 LBLE STO3 2 CHS 40 + COS/RCL3 9 SIN x/2 x/RCL1 × PRTX L3 CHS 40 + SIN RCL2 SIN STO5 CHS RCL3 2 CHS + 90 + SIN RCL3 2 x 9 × RCL1 × RCL3/RCL5 + SIN PRTX SPC 1/X>Y GTO7 RTN LBL7/RCL3 L6 GTOE RTN

References

Ehlers N & Kruse Hansen F (1971) On the optical measurement of corneal [illegible] *ophthal (Kbh)* 49 65–81

Ehlers N & Sperling S (1977) A technical improvement of the Haag Streit [illegible] *ophthal (Kbh)* 55 333–336

Jaeger W (1952) Tiefenmessung der menschlichen Vorderkammer [illegible] Platten (Zusatzgerat zur Spaltlampe) [illegible] *Graefes Archiv f Ophthalm* [illegible]

Mishima S & Hedbys B O (1968) Measurement of corneal thickness with [illegible] pachometer *Arch Ophthal (Chicago)* 80 710–713

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INFLUENCE OF TRANEXAMIC ACID AND ACETYLSALICYLIC ACID ON THE THICKNESS OF THE NORMAL CORNEA

BY

THOMAS OLSEN NIELS EHLERS and THORKILD BRAMSEN

In a masked cross-over study ten normal subjects were treated with tranexamic acid and acetylsalicylic acid one g three times daily for seven days The central corneal thickness was found to increase in response to acetylsalicylic acid and to decrease in response to tranexamic acid This finding provides evidence for the involvement of the fibrinolytic system in the regulation of the normal corneal thickness The endothelial morphology as seen with the specular microscope was unchanged during treatment with either drug

Key words acetylsalicylic acid – corneal thickness – endothelium – fibrinolysis – tranexamic acid

fibrinolytic treatment has been shown to reduce corneal oedema (Bramsen & ...rs 1977 Bramsen et al 1978 Bramsen 1978) while activation of fibrinolysis in ...ents with vitreous haemorrhages induces corneal oedema (Bramsen 1978a) ...cetylsalicylic acid has been shown to increase the fibrinolytic activity in normal ...jects (Menon 1970 Moroz 1977) Presumably because of this effect acetylsali... acid increases the risk of secondary haemorrhages in patients with traumatic ...haema (Crawford et al 1975) If fibrinolytic factors are involved in the ...ulation of the thickness of the normal cornea it might therefore be anticipated ...t acetylsalicylic acid treatment would increase the corneal thickness

The present investigation was undertaken in order to study the corneal thickness ...ponse to treatment with the antifibrinolytic drug tranexamic acid and acetylsali...c acid which has a fibrinolytic effect in normal subjects Because activation of

...ceived February 11 1980

fibrinolysis in the anterior chamber has been shown to cause [illegible] endothelium of bovine corneas (Morton & Turnbull 1964) the [illegible] appearance of the endothelium was also studied during this trea[illegible]

Subjects and Methods

The effect of tranexamic acid and acetylsalicylic acid on the corneal [illegible] studied as a masked trial Ten normal volunteers eight men and two [illegible] age range 24 to 28 years were given two pillbottles each One [illegible] Cyklokapron® tablets with 0 5 g tranexamic acid and the other Magnyl® [illegible] 0 5 g acetylsalicylic acid Each subject was instructed to take two [illegible] daily from one of the two bottles for seven days make a pause of [illegible] then take two tablets three times daily from the other bottle for another [illegible] The order of the treatment tranexamic or acetylsalicylic acid first, [illegible] made individually by the subject and not made evident for the examiner [illegible] each treatment period the central corneal thickness was measured [illegible] after noon with a modified Haag Streit pachometer (Ehlers & Sperl[illegible]) [illegible] measurement was the mean of three determinations each taken as the [illegible] reading on the pachometer Both eyes were measured and their mean [illegible] the thickness of the patient For a trained examiner the standard [illegible] single determinations of central corneal thickness with the present [illegible] been found to be 5–6 µm (about 1%) from a large number of [illegible] subjects After completion of the treatment period corneal thickness [illegible] drawn for each subject It was then judged by the examiners which of [illegible] periods were the tranexamic acid treatment period and the [illegible] treatment period respectively After that the true order of treatment [illegible] to knowledge

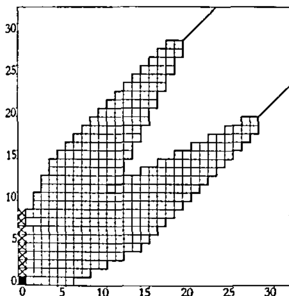
After completion of the masked study three other volunteers were [illegible] Cyklokapron® and Magnyl® in the same dosage as above The corneal [illegible] was examined with a non contact specular microscope (Olsen 1979) before [illegible] middle and after the seven day treatment periods

In four other volunteers the central corneal thickness was measured [illegible] described above for seven days without any drug treatment

Results

The masked study

In two subjects it was not possible to judge which of the two treatment periods [illegible] the tranexamic acid treated and the acetylsalicylic acid treated, respectively [illegible]



F g 1

ual analysis chart (°α = 0 1) Vertical step correct judgement on the acetylsalicylic acid and the tranexamic acid treatment periods

ning eight subjects the order of treatment judged by the investigators were l to be in concordance with the true order in all cases (Fig 1)

Fig 2 the mean corneal thickness of the subjects during the tranexamic acid he acetylsalicyl acid treatment period is shown In this figure all ten subjects included The central corneal thickness is seen to decrease in response to xamic acid ingestion During the first three days a slight tendency towards an ase may be noted after which a decrease is evident The opposite variations een for acetylsalicylic acid

thel um

specular microscopic detectable alterations in the corneal endothelium was d, either during treatment with tranexamic acid or with acetylsalicylic acid (Fig

normal corneal thickness variation

analysis of variance the mean day to-day variation (SD) in central corneal kness of the four subjects was found to be 0 0023 mm Using this figure the confidence limits for the mean spontaneous variation of ten subjects around

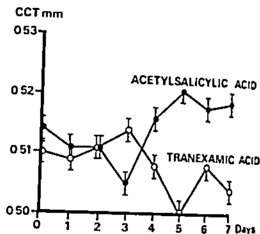


Fig 2

Mean value (± SEM) of the corneal thickness in ten normal subjects treated with acetylsalicylic acid and tranexamic acid.

Fig 3

The corneal endothelium in a 25-year-old man before (top), fifth day during [illegible] two days after (bottom) treatment with acetylsalicylic acid three g daily for [illegible]. On the fifth day of treatment a corneal thickness increase of 0.0[illegible] mm was found. No [illegible] specular microscopic appearance is noted. Bar = 100 μm.

ie mean would be expected to be 0 0023 mm (= 0 0023 × $t_{0\ 05}/\sqrt{10}$ three
›s of freedom) (by chance the same value) The observed increase and
ise from the initial mean in Fig 2 is seen to exceed this limit.

Discussion

resent study has shown that acetylsalicylic acid and tranexamic acid ingested
influence the normal corneal thickness

decrease in corneal thickness in response to tranexamic acid occurred after
to four days of treatment during which a slight increase was noted The
for this biphasic course is not clear Tranexamic acid has been shown to
ulate in the anterior chamber in a matter of hours after oral ingestion
isen 1979) Whether a further accumulation can occur after several days of
nent is unsettled

wever an improtant factor which may need consideration in the interpreta
f the observed time course is the possible counter reaction of the subject to the
nent. Assuming the involvement of the fibrinolytic system the observed lag
d of several days before a decrease in corneal thickness became evident may
plained by an initial compensatory decrease in the fibrinolytic activity of the
nism With time this counter regulation presumably becomes insufficient and
ffect of the antifibrinolytic treatment then breaks through If an initial
compensation occurs an initial increase in corneal thickness would be ex
ed.

ie above considerations are entirely speculative The importance of time in the
eal thickness response of the subject was however also found by Bramsen &
rs (1979) in a study of graft thickness

e corneal thickness response to acetylsalicylic acid treatment showed a similar
asic time course The mirror like effect of acetylsalicylic acid as compared to
l of tranexamic acid is strongly suggestive of a mechanism opposite to that of
examic acid This seems consistent with the fibrinolytic activity of acetylsalicylic
(Menon 1970 Moroz 1977) It has been shown (Nellemann Sørensen 1977)
salicylic acid enters the anterior chamber The inability to demonstrate any
ular microscopically detectable changes of the endothelium during treatment
cates that if the mechanism was to alter the permeability of this layer the effect
a physiological one rather than a toxic one

Whether the effect of acetylsalicylic acid and tranexamic acid on corneal thickness
mediated by an effect on the fibrinolytic system is still unsettled The fact that
tylsalicylic acid increases and tranexamic acid decreases thickness is however
couraging for a hypothesis of the involvement of the fibrinolytic system in the
ulation of the normal corneal thickness

References

Bramsen T (1978) A double-blind study on the influence of tranexamic acid on intraocular pressure and the central corneal thickness after trabeculectomy ... simplex *Acta ophthal (Kbh) 56* 998–1005

Bramsen T (1978a) The effect of urokinase on central corneal thickness ... haemorrhage *Acta ophthal (Kbh) 56* 1006–1012

Bramsen T (1979) Serum and aqueous humour concentration of tranexamic ... peroral administration *Acta ophthal (Kbh) 57* 455–460

Bramsen T Corydon L. & Ehlers N (1978) A double blind study of ... tranexamic acid on the central corneal thickness after cataract extraction ... *(Kbh) 56* 121–126

Bramsen T & Ehlers N (1977) Bullous keratopathy (Fuchs endothelial d...) ... systematically with 4 trans amino-cyclohexano-carboxylic acid ... 665–673

Bramsen T & Ehlers N (1979) Early post-operative changes in graft ... penetrating keratoplasty *Acta ophthal (Kbh) 57* 258–268

Crawford J S Lewandowski R L & Chan W (1975) The effect of ... traumatic hyphaema *Amer J Ophthal 80* 543–545

Ehlers N & Sperling S (1977) A technical improvement of the Haag Streit ... *ophthal (Kbh) 55* 333–336

Menon I S (1970) Aspirin and blood fibrinolysis *Lancet I* 364

Moroz L M (1977) Increased blood fibrinolytic activity after a ... *Med 296* 525–529

Morten R. W & Turnbull W (1964) The effect of intracorneal fibrin ... cornea *Amer J Ophthal 57* 280–287

Nellemann Sørensen P (1971) The penetration of quinine salicylic acid, PAS, ... barbital and lithium across the vitreous barrier of the rabbit eye ... 194–208

Olsen T (1979) Non-contact specular microscopy of human corneal ... *ophthal (Kbh) 57* 986–998

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ORNEAL THICKNESS AND ENDOTHELIAL DAMAGE AFTER INTRAOCULAR LENS IMPLANTATION

BY

THOMAS OLSEN and JENS SINDBERG ERIKSEN

The corneal thickness and the specular appearance of the corneal endothelium are reported in 100 patients with unilateral intraocular lens implantation Post-operative time ranged from one to 42 months An average central endothelial cell loss of uncomplicated cases of 46% range 1 to 83% with no correlation with time after the operation was found A significantly higher cell loss was found in cases with technical complications shallow anterior chamber or increased intraocular pressure post-operatively No correlation was found between the corneal thickness and the endothelial cell loss In two patients however with a cell density below 500 cells mm² a slight increase in corneal thickness was noted Thirty patients presented a guttate endothelium. Ir respective of the occurrence of surgical complications the presence of a guttate endothelium was found to be a major determinant of the corneal thickness increase and could be ascribed as a cause of persistent corneal swelling in six of twel e patients with elevated corneal thickness The progression of guttate changes occurred independently of the cell loss

Key words cataract extraction – cell loss – corneal thickness – endothelium – lens implantation – specular microscopy

ract extraction combined with an intraocular lens implantation is now be ing an increasingly employed surgical procedure Along with the good refrac correction it provides to the patient, this insertion of a foreign body into the eye its costs, however One of the feared complications is persistent corneal oedema. h seems to occur more frequently after lens implantation than after simple ract extraction (Jardine & Sandford Smith 1974 Pearce 1972 1975 Duffner

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et al 1976 Baggesen et al 1978) The incidence of corneal oedema [illegible] these studies ranges from a few per cent to 13% Other investigators [illegible] demonstrate this higher incidence (Binkhorst & Leonard 1967).

In recent years a number of specular microscopic studies have reported [illegible] endothelial cell loss associated with lens implantation than without lens [illegible] after cataract extraction (Bourne & Kaufman 1976 Forstot et al [illegible] 1977 Sugar 1979 Abbott & Forster 1979 Galin et al 1979) Some [illegible] not found this higher cell loss (Hirst et al 1977 Binkhorst et al [illegible] studies the cell loss after lens implantation ranges from 7 to [illegible] The operative follow up time however also varies considerably Because a [illegible] tion of the cell population occurs during the first months after the operation [illegible] al 1978 Sugar 1979 Galin et al 1979) this makes a direct comparison [illegible] studies difficult The lowering of the cell population has been viewed [illegible] concern because a low cell density presumably renders the cornea more [illegible] to the development of corneal oedema (Irvine 1956 Capella 1971 [illegible] Bourne & Kaufman 1976a Kaufman 1979)

The immediate post-operative increase in corneal thickness after lens [illegible] tion seems to be higher than after simple cataract extraction (Cheng et al [illegible] Praeger & Schneider 1977) Because of the quantitative association between [illegible] and immediate corneal thickness increase after cataract extraction (Olsen [illegible] this is to be expected In the above mentioned studies however corneal [illegible] was found to return to normal levels some months after the operation [illegible] remarkable that even in case of very high immediate increase in corneal [illegible] after surgery and therefore presumably a high concomitant cell loss [illegible] thickness has been reported to return to its pre-operative level [illegible] Cambiaggi 1956) It therefore seems that the long term effect of [illegible] loss on the corneal thickness still remains to be shown

The present investigation was undertaken in order to elucidate the [illegible] endothelium for the ultimate hydration of the cornea after cataract [illegible] lens implantation By this study it was attempted to throw light upon [illegible] unsettled question of the information yielded by the endothelial [illegible] significance for corneal hydration

Subjects and Methods

At the Central Hospital in Nykobing Falster cataract extraction with lens [illegible] been employed since 1976 in patients with senile cataract and more than [illegible] Indication for lens implantation has generally been found if the patient presented [illegible] history of uveitis no present eye inflammation corneal oedema or marked [illegible] dystrophy glaucoma retinal detachment juvenile onset diabetes [illegible] shallow anterior chamber

: ı surgical procedure was intracapsular cryoextraction with corneal incision Pre-opera -eatment consisted in diamox 500 mg intravenously and eye ball massage The lens used hout was a Federow iris clip lens (manufacturer 3M) No special lens coating solution ed to lubricate the lens prior to insertion. To obtain fixation of the lens dry pilocarpine applied to the wound edge Normal saline was used as irrigating solution if necessary d closure was done with 8–0 running Dexon® or Vicryl® absorbable suture All but a erations were done by one surgeon (E.W) Post-operatively the patients were treated ilocarpine eye drops and prednisolone ointments for six and one months, respectively

the present study only patients with an unoperated fellow eye without previous trauma ease other than cataract were included. In this way 140 patients with unilateral lens nt were selected from the operated series Eighteen patients had died since the tion. Nine patients could not be traced or did not show up for the present follow up gation. Seven patients were omitted due to poor general condition Four patients had seudophakos removed shortly after surgery due to dislocation of the lens and were ded from the study

the present follow up examination corneal thickness measurements were deferred (and lar microscopic examination not attempted) in two patients with clear corneas due to lity of the patients to fixate a target. One patient presented with an iridocyclitis on the ted side Because none of the other patients showed this complication this patient was ded from the below grouped data (the corneal thickness was 0 550 and 0 510 mm of ated and unoperated side, respectively and the cell loss was 4o on the operated side

us leaves 99 patients 39 men and 60 women in the age range from 69 to 91 years with a teral lens implant. Of these two patients had previou l undergone intracapsular act extraction whereas the rest of the patients had no pre ious history of disease or na in the now pseudophakic eye The time period from the operation to the present ination ranged from one to 42 months.

ta concerning complications that occurred during or after the operation were obtained spectively from the case record

ntral corneal thickness was measured with a modified Haag Streit pachometer (Ehlers & ling 19 7) Each measurement was taken as the closest 5 µm reading on the scale reading e pachometer Single determinations were used the standard de iation of which has found to be 5–6 µm from a large number of readings on several indi iduals Corneal kness of non-operated eye was taken as control In what follows residual corneal thickness ease refers to central corneal thickness of operated eye minus thickness of non-operated

he corneal endothelium was photographed with a non-contact specular microscope sen 19 9) in a central area of both sides and 2 3 mm superiorl in the operated eye If specular photomicrographs from the central endothelium re ealed one or more circular ects in the endothelial reflex larger than two cells width the endothelium was classified as ttate endothelium By using contralateral eye as control a cell loss was estimated as the centual decrease in cell count from unoperated eye

Results

ineal th ckness

ınty patients showed a guttate endothelium with bilateral involvement in 28 of e cases. Irrespective of the occurrence of surgical complications the presence of a

guttate endothelium was found to be an important factor for the [illegible]
As shown in Table I the guttate changes were worse (more [illegible]
defects in the endothelial reflex) in the operated eye in about two-th[illegible]
which were largely responsible for the increased thickness in this group

In order to further analyse possible factors influencing the corneal t[illegible]
patients were grouped as shown in Table II If per-operati e compl[illegible]
excessive vitreous loss or difficulty in lens placement had occurred, or a d[illegible]
of the lens had occurred post-operatively the patients were classified as [illegible]
complications The mean side difference in corneal thickness for this group [illegible]
different from the group of uncomplicated cases without guttate endoth[illegible]

Fourteen patients had a shallow anterior chamber post-operati ely The [illegible]
difference of this group differed significantly from the reference group (T[illegible]
Six of the patients however also had endothelial guttae and when these [illegible]
were withdrawn the mean side-difference diminished to 0 007 (± 0 0[illegible]
different from the reference group

The group with increased intraocular tension comprised patients w[illegible]
mentally treated ocular hypertension and patients with a tension higher [illegible]
mmHg found at the present follow up examination Although this group [illegible]
the highest mean side difference in corneal thickness the scatter was large [illegible]
P value just about the five per cent level Two patients in this group had [illegible]

Table I

B lateral comparison of endothelial dystroph and corneal thickness in 30 patients w th un lateral lens implant.

Specular m croscop c appearance	n	ΔCCT (x̄ ± S
Worse in operated eye	21	+ 0 03 (± 0 03
S milar involvement on both s des	8	+ 0 [illegible]5 (± 0 01
Worse in non-operated eye	1	0 01
Total	30	+ 0 [illegible] (± 0 [illegible]

ΔCCT central corneal thickness of opera ed eye *minus* th[illegible] of non-operated eye (mm)
* $P < 0.01$ by Mann Wh tney U est compared to sec nd group [illegible]

		n	Unoperated eye	Operated eye	Difference	Mann Whitney U test
No surgical complications	− guttate endothelium	19	0.[illegible]7 (∓0.0[illegible]6)	0.5[illegible] (∓0.0[illegible])	+0.00[illegible] (∓0.011)	
	+ guttate endothelium	18	0.[illegible]10 (∓0.0[illegible]7)	0.561 (∓0.013)	+0.021 (∓0.011)	$p < 0.05$
Technical complications		10	0.541 (∓0.015)	0.5[illegible] (∓0.0[illegible]4)	+0.011 (∓0.012)	n s
Shallow anterior chamber		11	0.5[illegible]0 (∓0.0[illegible]0)	0.532 (∓0.0[illegible])	+0.0[illegible] (∓0.031)	$p < 0.05$
Intraocular pressure > 22 mmHg post-operatively		10	0.[illegible]3 (∓0.0[illegible])	0.56[illegible] (∓0.082)	+0.038 (∓0.067)	p ~ 0.0[illegible]
Total		90	0.[illegible]30 (∓0.0[illegible])	0.[illegible]11 (∓0.041)	+0.011 (∓0.033)	

[illegible] indicates significant ($p < 0.05$) difference by Student's paired t test
The mean CCT difference was tested against mean difference of the first group listed
Two patients fell into two groups. One patient had lens dislocation and a shallow anterior chamber; one patient had lens dislocation and increased intraocular tension

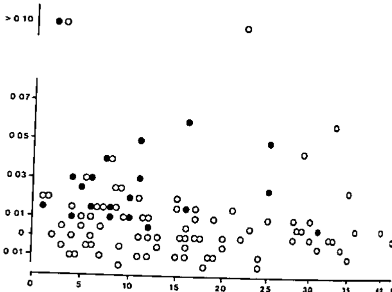


Fig 1

Central corneal thickness of operated eye minus central corneal thickness of u [illegible] (ΔCCT) plotted against time after unilateral lens implantation in 79 patients [illegible] signify patients with guttate endothelium appearing worse on the operated side [illegible] signify normal or non progressed guttate endothelium Dotted line indicates upper [illegible] of a group without complications and endothelial dystrophy

dystrophy which however was of similar appearance on the two sides, the [illegible] difference in corneal thickness being only 0 005 mm

No significant change in corneal thickness with time after the operation [illegible] found in the present series (Fig 1) When a group of patients with no [illegible] complications and without endothelial guttae was selected from the time [illegible] beyond six months the mean residual corneal thickness increase was found [illegible] + 0 005 mm (± 0 015 (SD) n = 42) which was significantly different from [illegible] not different from similar patients with shorter lens wearing time [illegible] group of patients free of complications and endothelial dystrophy as a [illegible] group the normal values for residual thickness increase could be said to [illegible] 0 035 mm (= mean value plus two standard deviations) (dotted line in Fig 1 [illegible] this way 11 of the patients could be said to have abnormal persistent [illegible] cornea with a central corneal thickness ranging from 0 [illegible] to 0 [illegible] operated eye 0 040 to 0 200 mm different from non-operated eye

T bl III

Ce t le l lel l ell l y (ell /) Jl p t w il l e lle gl t (e ∓ sl)

		n	U per te l eye	Operate l eye	Cell l s %	Unpaire l t test
No surgical complic itions	− guttate end thel um	49	? 86 (∓ 3(?)	11 (∓ 39)	− 11 9 (∓ 19 3)	
	+ guttate endothelium	14	2560 (∓ 388)	1396 (∓ 630)	− 48 1 (∓ 21)	l > 0 60
Technical complications		10	2384 (∓ 479)	1011 (∓ 37( )	− 57 7 (∓ 1? 6)	l < 0 0
Sh llow anterior ch mber		1?	2,81 (∓ 419)	949 (∓ 392)	− 63 5 (∓ 14 1)	l < 0 01
Intr ocul ir pressure > ?2 mmHg post operatively		8	? 61 (∓ 401)	9 4 (∓ 11)	− 6? 7 (∓ 1 8)	l < 0 0
Tot l		91	? (∓ 387)	1 (8 (∓ 1)	− 0 8 (∓ 19 3)	

* Me n cell loss comp re l with first group list l

C ell loss comp ired with the two first group c n b e l

Tw o p itients fell ii to tv o groups One patient had len di l c it on and a sh ll w anterior ch mber one p itient h d lens disloc ition and incre ised intr iocul ir ten ion

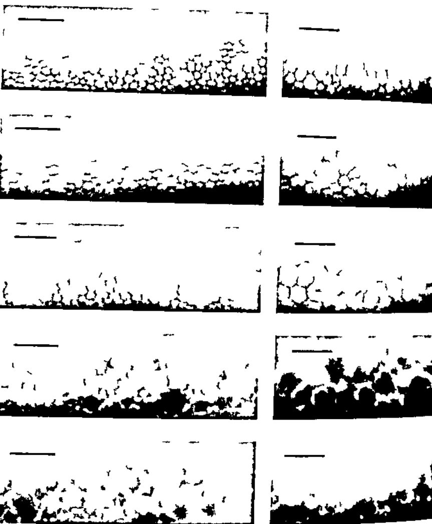


Fig 2
Central corneal endothelium in five patients with unilateral lens implant. Left pa d f non-operated eve right part operated eve Two patients at bottom of f re pre bilateral guttate endothelium with dominant appearance on the operated side. Bar 1

Cell loss

In Table III the data on central endothelial cell densities have been grouped same way as in Table II In eight of the patients bilateral endothelial cou not available due to poor quality of the photographs (1) ex essive d changes of the endothelium or marked corneal oedema (7) (see Fi 1 group with no surgical complications identical unoperated cell counts were

ose patients with or without guttate endothelium Since the central cell loss also not differ these two groups were pooled and compared to the group with plications These groups of technical complications shallow anterior chamber increased intraocular pressure all had a significantly higher cell loss than the group of uncomplicated cases Irrespective of the occurrence of complications mean cell loss of those with or without progression of dystrophic changes was % (n = 15) and 53 4% (n = 9) respectively (non significant)

Fig 3 the central cell loss of uncomplicated cases has been plotted against time the operation No significant relation was found The vertical difference in cell ity ie the difference between superior and central counts was also not ficantly related to the post-operative time ($r = -0\ 21$ $P > 0\ 05$) The highest es (about 60% lower density in the superior region) were however found ng the first four months The mean decrease in cell count from the central area he region 2–3 mm superiorly was 24% (± 20) of uncomplicated cases No elation was found to the age of the patient in the present series ($r = 0\ 19$ 0 05) A somewhat higher difference in vertical density was found in those ents with a guttate endothelium (33 4% vs 21 5% lower cell count in the rior region for uncomplicated cases with and without dystrophy respectively 0 07)

relation between cell loss and corneal thickness

was found between endothelial cell density and corneal thickness of perated eye ($r = 0\ 12$ $P > 0\ 05$ $n = 98$) No correlation was found between the

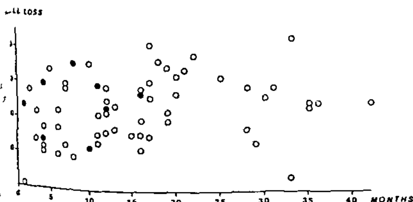


Fig 3

ntral endothelial cell loss of uncomplicated cases related to time after lens implantation Meaning of filled and open circles explained in Fig 1

Olsen T (1979) Non-contact specular microscopy of human corneal endothelium ophthal (Kbh) 57 986–998
Olsen T (1980) Corneal thickness and endothelial damage after intracapsular extraction Acta Ophthal (Kbh) 58 424–433
Pearce J L (1972) Long term results of the Binkhorst iris-clip lens in senile cataract Ophthal 56 324–331
Pearce J L (1975) Long term results of the Choyce anterior chamber lens [illegible] Ophthal 59 101–106
Praeger D L & Schneider H A (1977) Corneal thickness measurements [illegible] intraocular lens implantation Ophthal Surg 8 97–101
Rao G N Shaw E L Arthur E & Aquavella J (1978) Morphological appearance of healing corneal endothelium Arch Ophthal (Chicago) 96 [illegible]–030
Stocker F W (1971) The Endothelium of the Cornea and its Clinical Implications C Thomas Springfield Ill
Sugar A (1979) Clinical specular microscopy Surv Ophthal 24 [illegible]

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relation between cell loss and corneal thickness

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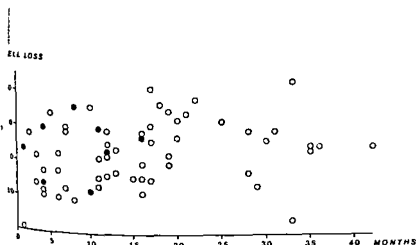


Fig 3

ntral endothelial cell loss of uncomplicated cases related to time after lens implantation Meaning of filled and open circles explained in Fig 1

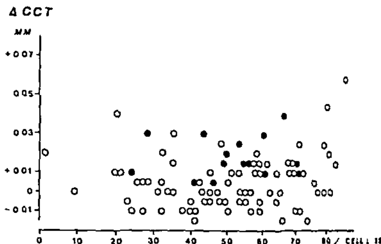


Fig 4

Percentual difference in central endothelial cell count (cell loss) related to difference in central corneal thickness (ΔCCT) between operated and non-operated side in 91 patients with unilateral lens implant Meaning of filled and open circles explained in Fig 1 ($r = 0.13$ $P \approx 0.9$)

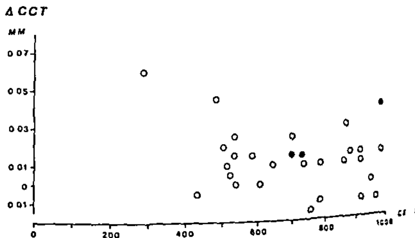


Fig 5

Correlation between residual corneal thickness increase and endothelial cell density in operated eye for cell densities below 1000 cells mm² Meaning of filled and open circles explained in Fig 1 ($r = -0.33$ $P = 0.09$)

loss and residual corneal thickness (Fig 4) Considering only very low cell [densities] no significant relationship was found either (Fig 5) However when the [indivi]dual points are considered in Fig 5 it is seen that two points with a cell density [bel]ow 500 cells/mm² fell above 0 035 mm the aforementioned upper normal limit [of t]he residual corneal thickness One of these patients (cell density 286 cells/mm²) [had] previously undergone an intracapsular cataract extraction After the secondary [len]s implantation she had a short period with a shallow anterior chamber and [len]s-cornea contact The operative course of the other patient was uneventful [No]ne of them had endothelial dystrophy or abnormal intraocular pressure

Discussion

[In] the present study the most important factor found to influence the corneal [thic]kness after lens implantation was the presence of a guttate endothelium [Pro]gression of dystrophic changes could be said to be the main factor responsible [for] persistent corneal swelling in six of the eleven patients with abnormal hydration [dete]cted in Fig 1 In the remaining five patients other factors had to be sought.

A remarkable result was that no significant correlation could be established [bet]ween the endothelial cell loss and the residual corneal thickness increase For cell [los]ses up to more than 80% or cell densities down to 500 cells/mm² there seemed to [be] absolutely no association between cell count and corneal thickness In two [pa]tients, however with a cell density below 500 cells/mm the cornea was somewhat [thic]ker on the operated side It cannot be excluded that these two patients thus had [a b]orderline function of the endothelium due to an inadequate number of cells

Considerations on the prevalence of a low cell density syndrome have to be made [wi]th due regard being paid to those corneas in which marked oedema hinders a [sp]ecular microscopic examination In two patients with normal endothelium on the [no]n-operated side the endothelium could not be studied due to severe oedema The [oe]dema in these patients had developed in parallel to the development of ocular [hy]pertension. As indicated in Table III an increased post-operative intraocular [pr]essure may add to the endothelial cell loss associated with the operation It is [th]erefore possible that in these two cases the intraocular pressure had caused a [fu]rther irreversible damage to the endothelium with corneal oedema as a result In [o]ne patient (residual thickness increase 0 04 mm) neither dystrophy low cell [d]ensity or inflammation could be associated with the corneal swelling the cause of [wh]ich thus remained uncertain

The majority of the patients showed a corneal thickness on the operated side [w]hich was close to that of the non-operated side The mean residual thickness

increase of uncomplicated cases without dystrophy of 5 µm although [illegible] significant is clinically an insignificant swelling and did not change [illegible] The cause of this swelling remains unknown A swelling of the same [illegible] has been found six months after intracapsular cataract extraction with a [illegible] *half* of that found in the present study (Olsen 1980)

The higher cell loss in the present study is strongly suggestive of a [illegible] immediate post-operative corneal thickness While performing the present [illegible] gation the corneal thickness of one patient was measured before and [illegible] after lens implantation An increase of 0 2 mm was found after [illegible] operation This is close to the double of the mean increase found in [illegible] mentioned study

The cause of the high cell loss associated with lens implantation needs [illegible] consideration Contact between the lens and the endothelium is one [illegible] factor (Kaufman et al 1977) The use of an air interface between the cornea [illegible] the lens during the operation has been shown to reduce the cell loss (Bourne [illegible] 1979) The duration of the operation is longer with lens implantation and [illegible] that time the endothelium is deprived a normal nutritive supply from the aque[illegible] humour The composition of the irrigating solution may be of particular [illegible] cance Calcium has been shown to be necessary for the integrity of the endothe[illegible] (Kaye et al 1968) and a Ringer solution or other enriched solutions [illegible] damage to the endothelium than normal saline (Edelhauser et al. 19[illegible])

What ever the nature of the technical improvements by which the endo[illegible] damage can be reduced the present study demonstrates that the patient [illegible] per se which must not be neglected One such risk factor is the presence of [illegible] endothelium It is remarkable that the progression of dystrophic endo[illegible] changes occurred independently of the cell density and the surgical cell [illegible] provocative factor which caused the progression of the dystrophic [illegible] remains speculative

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References

xt R. L & Forster R K. (1979) Cl n cal specular m croscopy and intraocular surgery
A Ophthal (Ch ago) 97 14 6 14 9

esen L H Land A M & N elsen N V (1978) Results from lens mplantation A
terial from Danish hospitals Acta ophthal (Kbh) 56 414 421

horst C D & Leonard P A M (1967) Iris-cl p pseudophakos implantation Amer J
hthal 64 947 956

horst C D Nygaard P & Loones L H (1978) Specular m cro copy of the corneal
dothelium and lens mplant surgery Amer J Ophthal 85 597 605

ne W M & Kaufman H E (19 6) Endothelial damage associated w th ntraocular
ses Amer J Ophthal 81 48 485

ne W M & Kaufman H E (19 6a) Cataract extraction and the corneal endothel um
er J Ophthal 82 44–47

ne W M Brubaker R F & O Fallon M (19 9) Use of a r to decrease endothe al cell
s during ntraocular lens mplantat on Arch Ophthal (Chicago) 97 1473 1475

lla J A (1971) The pathology of corneal endothel um Ann Ophthal 3 397 400

g H James A & Rubinste n B (1977) Corneal edema ris-cl p mplantat on and s mple
racapsular extract on compared Ophthal Surg 8 64 69

g H S urrock G P Rub nste n B & Bulp tt C J (1977a) Endothelial ce l lo s ar d
rneal th kness after intracapsular extraction and r s cl p lens mplantat n a r
mized controlled trial (interim report) Brit J Ophthal 61 785 790

ner L R. Wallace K W & St les W R (19 6) Copeland ntraocular er A n
hthal 87 590 593

hauser H F Van Horn D L Hynd uk R A & Schultz R. O (19 I ocula
gating solutions The r effect on the corneal endothel um A h Ophtha
8 657

rs N & Sperl ng S (1977) A techn cal impro ement of the Haag Stre t pachom ter A ta
hthal (Kbh) 55 333 336

tot S L. Ba kwell W L Jaffe N S & Kaufman H E (1977) The effect of nt a ocu
ns implantation on the corneal endothel um Trans Amer Acad Ophthal Oto ar ol
b 903

n M A. Lin L L Fetherolf E Obstbaum S A & Sugar A (1979) T me anal s of
rneal endothelial cell dens ty after cataract extract on Amer J Ophthal 88 93 96

rdini A & Camb aggi A (1956) Recherches sur l epa sseur corneenne apres extraction de
cataracte Ophthalmologica 131 41 50

u L W Sn p R C Stark W J & Maumenee E (1977) Quantitat e corneal e aluation n
tra cular lens mplantat on and cataract surgery Amer J Ophthal 84 775 80

ne A R (1956) The role of the endo hel um in bullous keratopathy Ar h Oph hal
hicago) 56 338 351

dine P & Sandford Smith J H (1974) Federov ris supported ntraocular acryl c lens Brit
Ophthal 58 718 724

ufman H E (19 9) The corneal endothel um Doc Ophthal Proc Ser 20 51 55

ufman H E Katz J & Valenti J (1977) Corneal endothel um damage w th ntraocular
enses contact adhes on between surgical materials and t ssue Science 198 525 527

e C I M sh ma S Cole J D & Kaye N W (1968) Stud es on the cornea VII Effects of
erfusion w th a Ca free med um on the corneal endothel um Inve t Ophthal 7 53 66

Olsen T (1979) Non-contact specular microscopy of human corneal endothel... Acta ophthal (Kbh) 57 986–998
Olsen T (1980) Corneal thickness and endothelial damage after intracapsular extraction Acta ophthal (Kbh) 58 424–433
Pearce J L (1972) Long term results of the Binkhorst iris-clip lens in senile cataract Ophthal 56 324–331
Pearce J L (1975) Long term results of the Choyce anterior chamber lens implant Ophthal 59 101–106
Praeger D L & Schneider H A (1977) Corneal thickness measurements intraocular lens implantation Ophthal Surg 8 97–101
Rao G N Shaw E L Arthur E & Aquavella J (1978) Morphological appearance healing corneal endothelium Arch Ophthal (Chicago) 96 2027–2030
Stocker F W (1971) The Endothelium of the Cornea and its Clinical Implications C Thomas Springfield Ill
Sugar A (1979) Clinical specular microscopy Surv Ophthal 24 21–32

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THE EFFECT OF TRANEXAMIC ACID ON SECONDARY HAEMORRHAGE AFTER TRAUMATIC HYPHAEMA

BY

L VARNEK[1] C DALSGAARD[4] A HANSEN[3] and F KLIE

During the period from March 19"8 to November 19"9 232 onsecuti e patients with traumatic hyphaema were allocated by admission-date t onser ative treatment and to treatment with the antifibrinolytic drug tranexamic acid.

Secondary haemorrhage occurred in only two out of 102 tranexam c a id treated patients while secondary haemorrhage occurred in 19 out f 30 conservatively treated patients This difference was statistically s gnificant

Some clinical aspects of the rebleeding cases are presented and briefly discussed

Key words traumatic hyphaema secondary haemorrhage incidence – severity – prevention by tranexamic acid

servatively treated traumatic hyphaema is complicated by secondary hae rhage (s h) in between 5–6% (Gregersen 1962) and 33% (Crouch & Frenkel 6) of the cases S h usually takes place between day 2 and 7 after the primary ma. (Gregersen 1962)

nce the secondary bleeding is often more severe than the initial haemorrhage l often accompanied by increased intraocular pressure and corneal staining s h requently associated with a poor visual prognosis (Gregersen 1962 Crouch & nkel 1976 Pandolfi 1978)

ecause of its antifibrinolytic properties the capacity of tranexamic acid in venting secondary haemorrhage after traumatic hyphaema has been studied ring recent years Favourable results seem to have been achieved in most reports ouch & Frenkel 1976 Bramsen 1976 1977 1979) although others have failed

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to demonstrate any statistically significant beneficial effect of tranexamic therapy (Kamp-Mortensen & Sjølle 1978).

The prospective study of Crouch & Frenkel (1976) includes patients with sickle cell trait, the existence of which might explain the high frequency of s.h. in this study. Nothing, however, is mentioned in the paper regarding the [illegible] frequencies of sickle cell trait in the tranexamic acid treated and [illegible] treated groups.

Bramsens conclusions on the effect of tranexamic acid (Bramsen 19[illegible]) [illegible] on combined retrospective and prospective studies with different treatment regimens at various periods in these parts of the study.

The material of Kamp-Mortensen & Sjølle (1978) also compares the frequency of s.h. in one group treated with tranexamic acid and one group treated [illegible] tively, not investigated simultaneously.

Based on the above, we found it relevant to perform a purely prospective [illegible] on patients with traumatic hyphaema referred to the four eye departments [illegible] Copenhagen sharing the casualty ward (Frederiksberg Hospital, Gentofte Hospital, Hvidovre Hospital and Rigshospitalet).

Material and Methods

Material

The material achieved from the four above mentioned departments [illegible] 232 patients (188 males and 44 females) with an average age of [illegible] years. [illegible] study, which took place from March 1978 to November 19[illegible], the patients [illegible] included consecutively.

Included into the study were all cases of traumatic hyphaema, which at the slit lamp examination showed either a sedimented hyphaema or [illegible] the anterior chamber, whereas patients with a haemorrhagic flare only were accepted for the study. Only patients admitted less than 24 h after [illegible] injury were included into the study. Other excluding conditions were [illegible] and perforating eye injuries.

Methods

All patients were treated as in-patients with bed rest and stenopaeic glasses [illegible] days. Tranexamic acid was given to patients admitted on even days in a dose of 25 mg/kg body weight three times daily for six days, while patients admitted on odd days received neither tranexamic acid tablets nor placebo tablets.

The tranexamic acid tablet treatment was initiated as soon after admission as possible. No patients had to stop the treatment because of disturbing side-effects of tranexamic acid.

› cut out placebo tablets was considered justified and ethical since the ›xamic acid induced persistence of the primary clot in the anterior chamber ›d unmask any placebo-blinding

ion of tranexamic acid treatment to admission-date was selected by ›ical reasons since the material had to be collected from four different ›tals By the same reason another statistical method than sequential sampling ›to be chosen for calculation of the results (Eaxact Fischer Test) 95% ›dence limits have been employed in the results

› admission the primary examination included examination of the visual › evaluation of the anterior chamber measurement of the intraocular ›sure ad well as ophthalmoscopy and evaluation of the accompanying lesions ›oscopy was not carried out routinely neither was evaluation of the coagulative of the blood

›ily determination of the size of the hyphaema was carried out On the 5th and ›day after the trauma all patients were reexamined

Results

›the total material the course was uncomplicated in 94% of the case le› ›ing ›tional defects

›able I shows the distribution of the average arithmetic values of the l › › › ›meters in the tranexamic acid treated group and the conservative› treated ›up visual acuity hyphaema size (in mm) at admission day and day fi› after he ›ma, age (in years) percentage of males and length of hospitalization (in day ›mentioned parameters of the two groups are very similar The only paramete› ›ing a differnce is the size of the hyphaema at day five after the trauma Since ›examic acid delays absorption of blood from the anterior chamber by maintain› the hyphaema in a clotting stage the greater average value of the residual ›haema size at day five after trauma in the tranexamic acid treated group than in ›conservatively treated group is understandable

›able II shows the lesions accompanying the traumatic hyphaemas in the ›examic acid treated and conservatively treated groups The severity of the ›mas in the two groups *evaluated from the accompanying lesions* is considered ›ual Average observation time was 12 days

›plications

›e most important complication was secondary haemorrhage

›Out of 10› tranexamic acid treated patients two patients (2%) developed s h ›ales) These s h both took place on day three after the trauma and their course

Table I

Different parameters in total series and in patients with secondary haemorrhage [illegible] plus b Distribution within *total series* of arithmetic mean values of [illegible] the tranexamic acid treated group (a) and the conservatively treated group (b) Columns a_{SH} plus b_{SH} distribution of the same parameters in [illegible] *haemorrhage* in the tranexamic acid treated group (a_{SH}) and the conservatively [illegible] (b_{SH})

	a 102	b 130	a_{SH} 9	[illegible]
Visual acuity day 1 after trauma	0 5	0 6	0 6	[illegible]
Visual acuity day 5 after trauma	0 9	0 9	1 0	[illegible]
Hyphaema size day 1 after trauma (mm)	2 0	[illegible]	1 0	[illegible]
Hyphaema size day 5 after trauma (mm)	0 [illegible]	0 1	s h	[illegible]
Age (years)	26 9	[illegible] 5	14 5	[illegible]
Sex (% males)	82 0	60 0	100 0	[illegible]
Length of Hospitalization Days	6 8	6 5	[illegible] 0	[illegible]
Length of control as out patient (days)	[illegible] 0	[illegible] 0	[illegible] 0	[illegible]

* Visual acuity at the last control

Numbers on top of columns indicate number of patients in the different groups

was mild without increase in intraocular tension or final visual defects [illegible] these patients did not differ significantly from the whole tranexamic acid group (see Table I)

Out of 130 conservatively treated patients 12 patients (9%) developed [illegible] males and one female) These s h took place on day two to seven after the [illegible] with maximum occurrence on day four (five cases) While these cases (see T[illegible] again initially did not differ significantly from the whole conservatively [illegible] group in respect to average values of the initial visual acuity the s[illegible] hyphaema and the sex and age the final visual acuity in this group was [illegible] worse (0 7 as compared to 0 9)

Table II

...ated lesions in total series (N 232) Tranexamic acid treated group left column ...servatively treated group right column Numbers in columns indicate percentages

% of patients	Tranexamic acid treated group (N 102)	Conservatively treated group (N 130)
...eal erosion and oedema	28	30
...natoma and wound of lids	10	19
... reactions	7	14
...ral retinal oedema	7	5
...nsient rise in IOP over 25 mmHg	8	5
...ysis of iris	2	5
...eous and Retinal Haemorrhage	5	4
...ocation of the lens without cataract	1	1
...umatic cataract	2	0
...tic nerve atrophy	1	0
...cular hole	1	0
...emocromatosis corneae	0	1
...tinal detachment	1	1

Table III

...ses and degree of visual impairment in cases of rebleeding in the gr... up ... nse... t ely treated patients with traumatic hyphaema For further discussi... n ... ee text

...laucoma treated with anterior chamber evacuation ...ght traumatic cataract	1 case (vision less than 0 1)
...laucoma and persistent anterior ...amber haemorrhage Psychosis	1 case (vision light perception)
...orneal haemochromatosis following glaucoma ...light traumatic cataract	1 case (vision 0 1)
...laucoma with transient corneal staining persistent ...treous haemorrhage psychic reaction	1 case (vision hand movements
Transient glaucoma and recession angle Choroidal rupture and transient corneal staining	1 case (vision 3/12)
Traumatic cataract	1 case (vision 6 9)

The average length of control for the 12 cases of s h occurring [illegible] conservatively treated group was 60 1 days ad compared to [illegible] days [illegible] conservatively treated group

The average period of hospitalization for the same 12 cases was [illegible] the average length of hospitalization for the whole conservatively treated group was only 6 5 days

In the conservatively treated group the s h were only mild with vision [illegible] to normal in six out of the 12 cases menationed The remaining six cases [illegible] severe course are presented in Table III The five of these six cases [illegible] increased intraocular tension above 30 mmHg for more than three days [illegible] two out of the six favourable cases developed a rise in intraocular tension [illegible] mmHg for 1–3 days

Additional remarks on complications

Although not included into this study because of the criteria for inclusion [illegible] nine patients were admitted to hospital during the study period with s h after [illegible] injuries Eight patients presented with s h on day two to four after trauma, and one [illegible] presented secondary vitreous haemorrhage six days after an unnoticed trauma [illegible] period one patient was admitted with a spontaneous haemorrhage in the anterior chamber

Discussion

Although only occurring in the minority of the cases of traumatic hyphaema (Gregersen 1962) s h should be prevented by the above mentioned reasons

Antifibrinolytic drugs have been suggested and tried in hyphaema treatment based both on their penetration into the aquous humour and on their successful employment since 1968 in the treatment of a number of systemic haemorrhagic conditions associated with hyperfibrinolysis (Crouch & Frenkel 1976 [illegible] 1978)

Since the positive hyphaema treatment results referred to in the literature are calculated from combined prospective/retrospective materials with [illegible] degrees of physical activities in the different parts of the studies (Bramsen [illegible] 1977 1979) and from materials including patients with sickle cell trait (Crouch & Frenkel 1976) these results all seem to be based on patient materials [illegible] equivalent than the present material

In the present study on 232 white patients who were all simultaneously treated with bed rest and stenopaeic glasses roughly half the patients in addition [illegible] cyklocapron at a dose of 75 mg/kg body weight orally daily for [illegible] reduction statistically significant at the 2% level (Exact Fischer Test) was demonstrated in the incidence of s h in the tranexamic acid treated group

he mild course of the two s h in the tranexamic acid treated group corresponds milar observations made by Crouch & Frenkel (1976)

he severe course of the six out of the 12 cases of s h occurring in the enatively treated group is in agreement with findings made by Gregersen 9) who reported increased intraocular tension with corneal staining and rrent bleeding in five of 11 conservatively treated patients with s h Crouch & kel (1976) reported a need of clot removal due to increased intraocular ssure and corneal staining in two out of nine conservatively treated patients with All three cases of s h reported by Kamp-Mortensen & Sjølie (1978) were ever mild without increased intraocular pressure or corneal staining

ased on the outcome of the present study a new prospective study had been ted, aiming to evaluate the safety of tranexamic acid therapy alone without ricted physical activities in the future therapy of traumatic hyphaema In this ly all the patients henceforward will be treated as in patients with tranexamic with further random division of the patients participating in the study into e treated with bed rest and those treated out of bed

References

nsen T (19 6) Traumatic hyphaema treated with the antifibrinolytic drug [illegible] *Acta ophthal (Kbh) 54* 250–256

nsen T & Ehlers N (1977) Bullous keratopathy (Fuchs Endothelial dyst [illegible]) [illegible] th systemically AMCA *Acta ophthal (Kbh) 56* 665–673

rsen T (19) Traumatic hyphaema treated with the antifibrinolytic drug [illegible] *Acta ophthal (Kbh) 55* 616–620

msen T (1978a) Effect of tranexamic acid on choroidal melanoma [illegible] 969

msen T (19 8b) The effect of urokinase on central corneal thickness and [illegible] emorrhage *Acta ophthal (Kbh) 56* 1006–1012

msen T (1979) Fibrinolysis and traumatic hyphaema *Acta ophthal (Kbh) 5* [illegible]

uch E R & Frenkel M (1976) AMCA in the treatment of traumatic hyphaema [illegible] phthal 84 335–360

gersen E (1962) Traumatic hyphaema *Acta ophthal (Kbh) 40* 199–199 200–201

dal T & Frisen M (1976) Tranexamic acid (AMCA) and late hyphaema A double blind udy in cataract surgery *Acta ophthal (Kbh) 54* 417–429

mp-Mortensen K & Sjølie A K (1978) Secondary haemorrhage following traumatic hyphaema A comparative study of conservative and tranexamic acid treatment *Acta ophthal (Kbh) 56* 763–768

mp-Mortensen K & Sjølie A K (1980) Traumatic hyphaema treated ambulatory without antifibrinolytic drugs *Acta ophthal (Kbh) 58* 125–128

ndolfi M (19 8) Intraocular haemorrhages a hemostatic therapeutic approach [illegible] phthal 22 322–334

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THE USE OF CONTACT LENSES IN WET OR DAMP ENVIRONMENTS

BY

PER LÖVSUND SVEN ERIK G NILSSON
and P ÅKE ÖBERG

The adhesion between the eye and a contact lens was recorded when influenced by water with varying salt concentrations Both active removal and spontaneous loss of hard and soft contact lenses applied to the eye were investigated
In environments with saline < 9 0 00 the risk of a soft contact lens falling out from the eye is almost negligible In environments with saline ≥ 9 0 00 the risk increases since adhesion in active removal decreased considerably In water based upon the investigations of spontaneous loss of contact lenses in an underwater environment well fitted soft lenses still do not however fall out of the eye It should therefore be possible to use well fitted soft contact lenses without any significant risk even in working conditions which may cause splashing of water upon the eye and regardless of the various salt concentrations of naturally occurring water in Sweden
For hard contact lenses independent of salt concentration adhesion in the underwater environment is extremely low and such lenses cannot therefore be used on an unprotected eye in conjunction with for example swimming The risk of them falling out under splashing with water upon the eye is clearly greater than for soft lenses

Key words contact lenses – adhesion – wet environment – water sports hazards – worker s safety

The considerable increase in the use of contact lenses had made it necessary to analyse the risks and advantages of such lenses under various working conditions and in various sports Previously animal experiments have been carried out

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estigate danger in conjunction with electric welding (Lovsund et al. 1979a) and -a-red heaters (Lovsund et al 1979b)

The question of the use of contact lenses in wet and damp environments is resolved The problem is seldom discussed in reference literature although the s of losing both hard and soft lenses in conjunction with water sports have been ssed (Hales 1978) The possible risk for personnel on fast, open customs cruisers of losing contact lenses by heavy splashing with water upon the eyes has been ussed extensively among authorities and at present such employees in Sweden not permitted to use contact lenses when on duty A couple of practical eriments with contact lens users on boats have been conducted but these have been of such a type and scope to enable any definite conclusions to be drawn e question is therefore still unsolved Since it also involves a number of other rking areas and sports in wet or damp environments it is important that scientific dies be carried out to provide a firmer basis for establishing for example ulations concerning requirements for employment and exemption granting

n this study adhesion between the eye and a contact lens has been recorded en affected by water with varying salt concentrations The project has compr ed estigations of I active removal and II spontaneous loss of contact le es plied to the eye Both hard and soft (low and high water content) lenses ha e en investigated

Material and Methods

Active removal of contact lenses applied to the eye

hen recording the adhesion between a contact lens and the corneal epithelium used contact lenses with a suture thread glued on to the centre of the lens The s was pulled away from the eye using an electric motor and the tensile force was gistered. The force at the moment at which the contact lens separated from the e was taken as measure of the adhesion

Table I
Contact lenses used

Study No	Lens-make	Material	Water content (%)	D opter	Diameter (mm)
I,II	Soflens	HEMA	39 (soft)	approx +1ɔ	13 6
I,II	Scanlens	PMMA	approx 1 2 (hard)	approx −ɔ	9 6
II	Soflens	HEMA	39 (soft)	approx −ɔ	13 6
II	Scanlens	HEMA	8ɔ (soft)	approx +1ɔ	13 ɔ

The investigation involved five volunteers (two men and three women [illegible] one regularly wore contact lenses (No difference appeared between the [illegible] the regular user of contact lenses and the subjects who did not use them The contact lenses which were individually fitted by a a contact lens technician were [illegible] two types hard lenses and soft lenses with low water content (Table [illegible] The volunteers were given Novesin® 0 4 % eye drops as topical anaesthesia which made it possible for the test subject to keep his eyes open and to reduce eyelid [illegible] to a minimum Between the various experiments the lenses were cleaned [illegible] disinfected in the prescribed way A 0 09 mm suture thread (Ethicon [illegible] 707G) was glued to the centre of the front of the lenses using a silicon glue [illegible] Medical Adhesive Silicone Type A Dow Corning) The glue was applied [illegible] uniformly as possible to the different lenses and the least possible amount was [illegible] in order to minimize deformation of the lens The glue could not be [illegible]

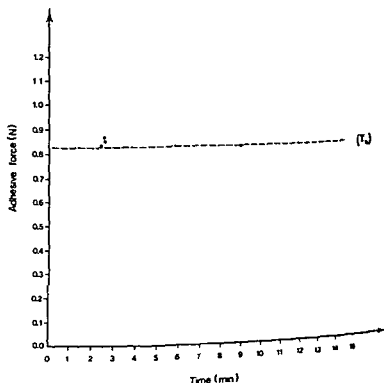


Fig 1

All recordings of adhesive force between cornea and contact lens and the [illegible] active removal of soft contact lenses when affected by water with salt [illegible] 1 7 and 8 0 00 or in air (53 pull distributed among 5 volunteers)

ere sufficiently firmly to high water content soft contact lenses and these are ...efore excluded from this part of the investigation

... rom the contact lens the suture thread went to a force transducer from which a ... ner thread was attached to the shaft of a motor The force tranducer ... tromed Limited) consisted of an unbonded strain gauge element with a ... ximum load range of ± 2 27 N The force transducer was bridge coupled and ... signal amplified (AC Carrier Preamplifier HP) and registered on a recorder ... cillographic chart recorder HP) A DC motor (Escap) fitted with a gear box ... ng a reduction of 2048 1 was used to pull the contact lens from the eye A ... stant speed (0 6 mm/second) was maintained during the entire pulling cycle In ... er to expose the eye and the contact lens to water with various salt concentra... ... s a plastic film intended for covering around a surgical operation area ... n-Drape® 3M) was used The film had a central hole 63 mm in diameter

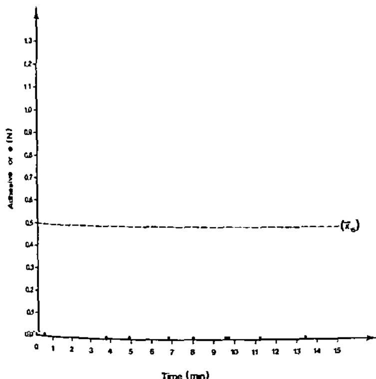


Fig 2

... recordings of adhesive force between cornea and contact lens and the mean of these in the removal of soft contact lenses when affected by water with a salt concentration of 9 0 00 (40 pulls distributed among 5 volunteers)

surrounded by an area with an adhesive coating which allowed the [illegible] attached to the skin around the eye of the supine volunteer The edges of the film were then folded up and attached to a ring placed above the head of the [illegible] subject This arrangement provided a watertight receptacle for the [illegible] solutions The receptacle was filled to the same level each time

The salt solutions were prepared from distilled water and NaCl and were kept at room temperature (23–24 C) during the experiments Recordings were made [illegible] salt concentration at 0 1 1 7 8 9 10 11 13 and 25 0 00 and also in air [illegible] any liquid other than normal tear flow

The lens was always applied to the right eye and in the same way [illegible] air bubbles were allowed between the eye and the lens and it was checked that the lens really was attached to the eye When the salt solution was poured into the plastic receptacle the pulling could start After the lens was pulled away the solution was removed and the lens could be applied to the eye again The registrations were continued during an effective time of 15 min in each [illegible]

II Spontaneous loss of contact lenses applied to the eye

In order to study whether or not contact lenses spontaneously fall out [illegible] in the underwater environment without any tensile force the volunteers [illegible] their faces in the various salt solutions for a period of maximum 15 min They were instructed to blink frequently and in between blinking to open the eye [illegible] perform eye movements in various directions If the lens fell out of the eye the [illegible] when this occurred was recorded The volunteers used snorkels for breathing The study comprised the same volunteers as in Test I Apart from the contact lenses used in Test I soft high water content lenses were also used (Table I)

Results

I Active removal of contact lenses applied to the eye

Soft low water content lenses

With regard to the force necessary to pull away the lenses from the eye [illegible] significant differences ($P \leq 0.05$) were recorded for the various salt concentrations $\leq$ 8 0/00 (0 1 1 7 and 8 0/00) either among themselves or between the solutions and air All these measurements are therefore shown in Fig 1 At 9–10 0/00 the [illegible] value for adhesive force began to fall at the same time as the individual measurements showed a large dispersion (Figs 2 and 3) At salt concentrations $\geq$ 11 [illegible] (11 13 and 25 0/00) adhesion was very low and without any significant differences

005) among themselves (Fig 4) A summary of the results for all salt concentrations is shown in Fig 5

In order to clarify further the relationship between salt concentration and adhesion a number of experiments were carried out in which the salt concentration was first increased in steps of 1 0/00 from 7 to 11 0/00 and then decreased directly to 7 0/00 A typical experiment from this series is shown in Fig 6 With regard to the different concentrations the adhesion picture generally agrees well with the result for the entire group of volunteers (Figs 1–5) At 7 and 8 0/00 the values are stable at a high level At 9 and 10 0/00 the dispersion in the measurements is large and the mean is clearly lower At 11 0/00 the mean falls further Upon a return to 7 0/00 the adhesion value rises to a level which corresponds approximately to the situation at the beginning in 7 0/00 concentration

Hard lenses

The adhesive force for hard lenses was considerably lower than for soft lenses In measurements in air i e with normal tear flow over the eye adhesion was recorded

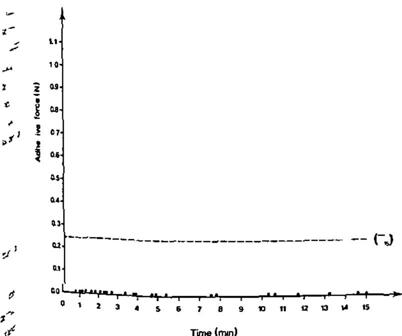


Fig 3
Recordings of adhesive force between cornea and contact lens and the mean of these in the removal of soft contact lenses when affected by water with a salt concentration of 10 0/00 (70 pulls distributed among 5 volunteers)

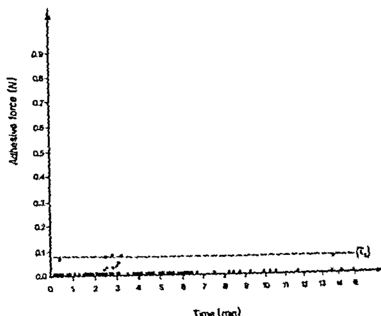


Fig 4

All recordings of adhesive force between cornea and contact lens and the mean d... active removal of soft contact lenses when affected by water with salt concentra... and 25 0 00 (105 pulls distributed among 5 volunteers)

as 0 09 ± 0 01 N In tests with water with various salt concentrations adhesive extremely low (< 0 01 N) independent of the salt concentration.

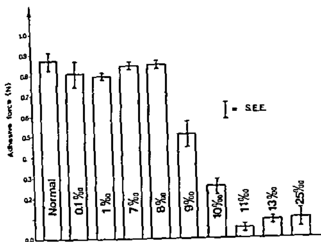
II Spontaneous loss of contact lenses applied to the eye

Soft low and high water content lenses

Not a single lens fell out during the 15 min test period despite frequent ... blinking and eye movements The salt concentrations were 0 1 9 and 25 0 ... concentration of 0 1 0/00 the lens on occasion adhered so firmly to the eye could not be removed until after dropping 9 0 00 saline for about 5 min. Fo... per lens type at each concentration for each of the five volunteers.

Hard lenses

All the lenses fell out at all salt concentrations (0 1 1 3 5 7 8 9 and 25 ... a mean time of about 1 min No definite difference in mean time was ob... between the various salt concentrations Four trials at each concentration f... of the five volunteers



F g 5

nean of the adhes e force between cornea and soft contact lenses when affected b with ary ng salt concentration or in air (normal) (5 volun eers) SEE standard err the est mate)

Discuss on

enses

study shows that salt concentration exerts a clear influence on the adhes n een soft contact lenses and the eye From firm adhes on at salt concentrat o 0 00 the values became highly variable at 9 and 10 0 00 while the adhesion wa ughout considerably lower at salt concentrations ≥ 11 0 00 The change in sion seems however to have not so much practical importance as was at first ght, since the soft lenses did not fall out spontaneously from the eye in the ments in underwater environment (Test II) which simulate real ty better lenses d d not fall out even after vigorous and frequent blinking and eye ements. It should however be emphasized that the experiments were carried using well f tted lenses There would appear to be a substantial risk of less rately f tted lenses falling out of the eye in water with a salt concentration ≥ 9 l The same risk may arise in conjunction with certain pathologically changed eas, e g in keratoconus In these cases however hard contact lenses are ually used

he question arose as to whether prolonged exposure to water alone irrespective salt concentration could change the corneal surface e g by washing away its ting so as to prevent adhesion of a contact lens The experiment shown in Fig 6

Acknowledgements

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References

Hales R. H (1978) Contact lenses. A Clinical Approach to Fitting, Williams & Wilkins Baltimore

Kloow G & Lindqvist T (1973) Vattnet i vara simbassanger (En fysikalisk undersokning) Institute of Physics, Uppsala University Sweden (In Swedish)

Kloow G (1979) Personal communication.

Lovsund P Nilsson S E G Lindh H & Oberg P A (1979a) Temperature changes in contact lenses in connection with radiation from welding arcs. *Scand J Work Environ Health* 5 271–279

Lovsund P Nilsson S E G & Oberg P A (1979b) Temperature changes in contact lenses in connection with radiation from infrared heaters. *Scand J Work Environ* 280–285

Waern M (1950) Algological excursions to the middle part of the Swedish east coast International Botanical Congress, Stockholm Excursion Guides

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SPHEROID DEGENERATION OF CONJUNCTIVA AND CORNEA

Two Years Follow Up

BY

MOGENS NORN

Twenty six subjects with spheroid degeneration were followed up after two years The number of colourless conjunctival droplets was seen to ha e increased by on an average 46% (2α = 0 05) and that of autofluorescent conjunctival droplets by 223% (2α < 0 01)
Counting within the individual sites disclosed that some droplets will disappear (not less than 30 and 21% respectively) while recently formed will consut at least 76 and 243%
The number of areas with band shaped keratopathy was found to rs to 26 ($P < 0\,001$) out of 104 possibilities (nasally and temporally of r ch left eye)
Vital staining (fluorescein rose bengal tetrazolium alcian blue) showed epithelium above the droplets to be intact and the droplet-containin e were found not to be abnormally dry (break up time tear production)

Key words degeneration spheroid – keratopathy bandshaped – conjunctu a cornea – break up time

heroid degeneration of cornea and conjunctiva implies the presence of ball ped elements in the exposed region concerned Such droplets range in size from small as to only just be visible under × 10 magnification with the Haag Streit slit p up to 400 µm They are generally limpid more rarely yellowish and tofluorescent Under direct lighting the distant half of the droplet is luminous ile the proximate half is shaded owing to the refractive index of the droplet mpared with that of its surroundings

The droplets may be so numerous on the cornea as to form bands along the bus, or possibly across the cornea. The phenomenon is then called Bietti s dular dystrophy climatic droplet keratopathy or Labrador keratopathy

ceived February 18 1980

In a previous study (Norn 1978) the author noticed that spheroid degenera... most frequent on the conjunctiva These patients have been summoned fo... follow up examination to see whether such droplets increase in number T... seemed to be the case the prevalence rising with increasing age to fall ag... however after the age of 70

Material and Methods

The initial series comprised 33 patients with spheroid degeneration found am... 810 Copenhageners

Of these 26 were summoned to a follow up examination two years later (two died and five could not be traced) They all attended the examination in morning at the eye department

The examiner was the same in all cases and proceeded in the same manner the initial examination (see Norn 1978)

In addition the eyes were examined for precorneal fatty layer by the interfer... method (Norn 1979b) BUT (break up time) tear secretion (lacrimal n... test) and by means of different vital stains mentioned in succession fluores... rose bengal tetrazolium and alcian blue mixture and possibly alizarin (Methods see Norn 1974) The results were compared with those of correspon... examinations of the contralateral normal eye

Table I

	Initially	Follow up		
		Mean	Increased	Reduced
Conjunctiva				
Lipid	645	943*	493	195
Autoflu	53	171**	199	11
Cornea				
Microcysts (ca)	180	5055	4875	0
Lipid	9	11	11	9
Autoflu	3	7	5	1

Change in number of droplets after two years The figures indicate the number of ph... per subject (26 subjects)

* $2\alpha = 0{\cdot}05$ ** $2\alpha < 0{\cdot}01$

Table II

	Initially	Follow up		
		Mean	Increased	Reduced
ictr a				
pid.	44	56	15	3
toflu.	31	39	15	-
a				
rocysts (ca.)	3	26	23	0
pid	2	2	9	9
toflu.	2	3	9	1

er of sites with spheroid degeneration A total of 104 sites (nasally and temporally of and left eye four areas per subject. 26 subjects examined)
0 001

Results

u ctiva

number of colourless droplets rose by 46% in the course of two years The rise significant (non parametric Mann Whitney rank sum test $2\alpha = 0\ 05$)

he number of autofluorescent droplets rose by 223% This rise was likewise ficant ($2\alpha < 0\ 01$)

he mean values have been set out in Tables I and III

ch of the 26 subjects had four areas examined (nasally and temporally of *right left* eye) a total of 104 sites The proportion of sites showing droplets increased in two years but the difference is not significant (Table II) In some instances plets disappeared from one area, while new ones might appear in a hitherto plet free region

Table III

	Initially	Follow up
Conjunctiva		
Limpid	24 8 ± 9 0	36 3 ± 8 4
Autoflu	2 0 ± 0 4	6 6 ± 2 4
Total	26 8 ± 9 4	42 8 ± 9 4

Change in number of conjunctival droplets after two years Mean values (± SEM) per subject, a total of 26 subjects

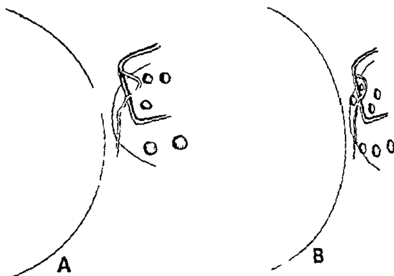


Fig 1A
Initial examination of case with four autofluorescent (hatched) and one limpid droplet pinguecula

Fig 1B
Shows the same site two years later The two autofluorescent droplets within the bend large vessel have disappeared The two others still exist below the vessel and a new o appeared closer to the limbus corneae A total of three autofluorescent and four droplets

Table I (two right columns) illustrates 1) the numbers of droplets noticed areas and 2) areas from which previously present droplets had disappeared.

In one case droplets were mapped out within one region by means of the of some blood vessels Fig 1 illustrates the result

The variations were greater than the calculations in Table I indicat droplets occurred within the same area while old ones disappeared Co droplets became autofluorescent while some fluorescent droplets were see this property The variations were independent of occupation or retirement

Cornea

Limpid and autofluorescent droplets were present in few cases only Such increase significantly in number (Tables I and II)

Band shaped keratopathies consisting of fine microspheric granules significantly in number (Table II t test $P < 0.001$) from three in two pati in nine patients These bands were all localized vertically along the limb

Table IV

	With spheroid	Control eye
Præcorneal fat (nm)	114	124
Break up time (sec)	23 0	?0 4
Tear production (dilution/5 min)	261	205
Rose bengal vital staining score*	3 9	? 5

Surface phenomena in 40 eyes with conjunctival spheroid degeneration compared with the conditions in 12 contralateral eyes (mean values)
* maximum 15 per eye

not yet grown towards the centre representing in other words grade I eneration according to Freedman s classification (Freedman 1965)

he corneal droplets were most often localized within areas showing micro-eroids (in four out of six cases)

s stated above the droplets differed in size (from 30 to 400 µm) There was ne eption however who presented a 3 mm long streak along the limbus conjunc e The lower one third of this was autofluorescent while the upper two-thirds e limpid constituting presumably a conglomeration of many droplets

face Phenomena

shown in Table IV the fatty layer covering the precorneal film and the stability the film (BUT) proved to be independent of the presence of pheroid generation of the conjunctiva and the mean values did not differ from these of a rmal series

The tear production was perhaps slightly reduced in eyes with droplets and the inability by rose bengal in the exposed part of the eye correspondingly increased wever the difference from the control eye was not significant and the results re within the normal range

al Staining

se bengal did not specially stain the epithelial regions covering the droplets n the other hand some pingueculae were stained diffusely (43% out of 80 ngueculae) particularly such as were elevated Vital staining by fluorescein reach of epithelial continuity) tetrazolium (degenerate enzyme holding epithelial lls) alcian blue (mucus) and alizarin red (calcium) did not differ from the nditions in a normal series In particular these dyes did not specially affect the oplets

Occupation

Two-thirds of the subjects had mainly outdoor work (sailor gardener pavour navvy surveyor cemetery attendant) and one third indoor work (office, clea..g, nursing)

Discussion

Spheroid degeneration was first detected on the cornea Frauenfelder et al (197.) also noticed such droplets on the conjunctiva Garner et al (1976) and Norn (19..) found the conjunctival site to be much more frequent than the corneal site

The *pathogenesis* is obscure *Corneal* spheroid degeneration is most frequent in the geographic regions having an intense ultraviolet light (the Red Sea Labrador).

The following facts go to show that *conjunctival* droplets also are provoked by ultraviolet light The geographic difference in prevalence between Greenland and Copenhagen (Norn 1978) the high incidence of pingueculae (Norn 19..a) which likewise is supposed to be caused by ultraviolet light and the predominance of outdoor occupation even though the present screening material comes from a c..

The droplets are localized within exposed areas both on the conjunctiva and on the cornea Dessication might therefore be conceived to be a contributory cause

However the results of the present investigation (BUT vital staining) ar.. against this theory

The follow up showed the number of droplets to have increased rapidly w.. two years Some droplets had disappeared within the same period Thus we get an impression of a variegated picture with development of many new droplets. Lar.. droplets become yellow and autofluorescent while others lose their colour an.. some even disappear completely

This disappearance was a quite new and unexpected observation The possibility might be conceived of a loss through the epithelium However vital staining afford.. no evidence to support this view (no epithelial cell damage breach of continuity nor mucus coating) The refractive index of the droplets may perhaps alter t.. equalized with the surroundings or the droplets may become so much reduced i.. size as to become unrecognizable (< 30 µm)

The *prognosis* of conjunctival spheroid degeneration is usually good the affectio.. being harmless with no subjective complaints Yet persons with droplets on th.. conjunctiva are subsequently liable to develop band shaped keratopathy as wel.. presumably in most cases concentrated peripherally In few cases only will th.. droplets spread across the cornea to form the rare type III with considerab.. impairment of the central vision

ı the presence of band shaped keratopathy the finding of droplets in the junctiva is of value in the *differential diagnosis* In cases with band shaped areous deposits decalcification is obtainable by tetracemine disodium (EDTA) s treatment has no effect on band shaped spheroid degeneration
le have started electronmicroscopic examinations of conjunctival droplets uding follow up examinations of the biopsy site

References

ınfelder P T Hanna C & Parker J M (1972) Spheroid degeneration of the cornea and onjunctiva *Amer J Ophthal* ,4 821–898
edman A (196ɔ) Labrador keratopathy *Arch Ophthal (Chicago) 74* 198–202
ner A Fraunfelder F T Barras T C & Hinzpeter E N (19‾6) Spheroid degeneration f cornea and conjunctiva *Brit J Ophthal. 60* 473–478
n M S (19,4) External Eye Methods of Examination p 200 Scriptor Copenhagen
n M S (19,8) Spheroid degeneration of cornea and conjunctiva Prevalence among skimos in Greenland and Caucasians in Copenhagen *Acta ophthal (Kbh) 56* ɔ1–56?
n M S (19 9a) Prevalence of pingvecula in Greenland and in Copenhagen an its *elation to pterygium* and spheroid degeneration *Acta ophthal. (Kbh) 57* 96–10ɔ
m M S (19,9b) Semiquantitative interference study of fatty layer of precorneal film A *ta phthal. (Kbh) 57* ,66–,74

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GALACTOSAEMIA WITH CATARACT AND PERSISTENT HYALOID ARTERY

A Clinicopathological Case Report

BY

P VANGSTED

A boy with galactosaemia and bilateral cataract developed large intraocular haemorrhages in the left eye which was enucleated
Histologically a persistent hyaloid artery was demonstrated This combination with galactosaemia seems not to have been described in the literature before. The haemorrhages are most likely secondary to the persistant hyaloid artery system In addition some foci of extramedullary haemopoiesis were demonstrated in the retina

Key words galactosaemia – arteria hyaloides persistens – retinal extramedullary haemopoiesis

We have recently investigated a case of galactosaemia with some peculiar findings which appear not to have been described before

Clinical History

The patient was a 10 month-old boy the third child in a family without kno n consanguinity, congenital (inborn) errors of metabolism or other malformations In 1968 the mother had borne a premature girl weight 1200 g who died after 24 h (no autopsy) In 1969 during the last month of her second pregnancy the mother had slight hypertension but the delivery

Presented by S Ry Andersen and O A Jensen at the 18th Annual Meeting at the European Ophthalmic Pathology Society Brussels 1979

Received March 10 1980

Table I
Laboratory findings at first examination

	Findings	Normal values
tose	310 mg/100 ml	0
tose (Thin layer chromatography)	+++	0
tophan (Thin layer chromatography)	+	0
sine (Thin layer chromatography)	+	0
inuria	+	0
tose 1 phosphate	658 μgr/ml eryth	0
tose 1 phosphate uridyl transferase	2 5 μmol UDPG pr h g Hb	27 6±3 ˜ (x̄±SD)
line phosphatase	1700	13-38
phosphatase	28	2 ˜ 10
ine amino-transferase	90	5-25

ere normal. Examination of the mother revealed monolateral squint wi h amb malformations During the last trimester of the recent pregnancy the m t loss of weight. Uncomplicated delivery in November 1977 in due time length 49 cm The boy did not thrive and after a few months the m e non-reacting left pupil In April 19 8 the 5-month-old child was tric Department of the Rigshospital because of suspected retinobla r was found and among others the following laboratory examinations ner 1)

agnosis of galactosaemia was established and the child was put on a g act se mmediate improvement of the clinical condition and the abnormal laborato

Ophthalmological Findings

eye

t nystagmus corneal diameter 11 mm slight posterior cortical and nuclear act. Behind the lens a persistent tunica vasculosa was noticed but normal us and no persistent hyaloid artery Electroretinogram (ERG) and ocular on normal

ye

eal diameter 10 5 mm flat anterior chamber and a dilated pupil with ounced ectropion uveae simulating partial aniridia A small lens with anterior ular cataract, nuclear and posterior cortical cataractous changes A retrolental

white to yellowish brown membrane was noticed transillumination reveal... shadow downwards The ERG was extinct tension slightly encreased. Ultraso... examination supported the diagnosis of congenital membrane anteriorly ... vitreal haemorrhages

Five months later the cataract in the right eye had diminished and the tu... vasculosa had disappeared The left eye was blind the lens was now subluxa... downwards still cataractous and a massive grey black membrane was no... behind the lens Ultrasonic examination (A & B scanning) now suggested a ... lesion in the posterior half of the blind eye which was enucleated

Ocular Pathology

Macroscopical examination (Eye Path Inst no 662/78)

The eye measured 21×19×19 mm the corneal deameter 10×10 mm. The ... was maximally dilated Vertical sectioning the lens was cataractous and ... haemorrhages were seen in the upper half of the eye Inferiorly a greenish ... The disc and the short optic nerve were punched out and cut with serial sec...



Fig 1

Eye Path Inst No 662 78 Extreme proliferation of iris pigment epithelium co... anteriorly and invading the chamber angle (arrow) Connective tissue in the anterior ... (large arrow) Haematoxylin-eosin stain (x 11?)

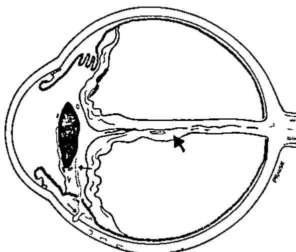


Fig 2

ematic drawing of the sagital section of the enucleated eye Totally detached retina (large w) Inferiorly the persistent hyaloid artery anastomoses with an artery in the ciliary body and sclera

Fig 3

rsistent hyaloid artery on its way to the anastomosis n the ciliary body (arrows) Haematoxylin phloxine saphranine sta n (× 98)



Fig 4
Extra medullary hemopoiesis in the retina (arrow) Haematoxylin eosin stain (x

anterior to and in the area of the lamina cribrosa About 225 sections of th
were cut including some sections of both calottes

Microscopical examination

Slightly diminished eye with dome shaped cornea The anterior chamber n
centrally due to posterior subluxation of the small lens Peripherally the cham
flat due to an enormous ectropion of the iris with anterior synechia to the c
The iris pigment epithelium continues on the anterior surface of the iris s
(Fig 1) The chamber angle is filled with fibrovascular tissue from the iris st
and some iron positive macrophages and lymphocytes are noticed Schlemm
is present but partly occluded There is slight capsular cataract anterior
posteriorly The lens epithelium is partly two-layered anteriorly and con
whole cortex including the posterior part where a few bladder cells (Wed
are seen

The lens is completely surrounded by a fibrovascular membrane with re
of haemorrhages The vitreous is small triangular and contains a large pe
hyaloid artery which anastomoses with an artery in the ciliary body inferiorly
and 3) The hyaloid artery can be traced back into the middle of the funnel-

ly detached retina Superiorly an oral retinal tear is noticed in some sections retina is degenerated with enormous gliosis and some foci of extramedullary opoiesis are seen (Fig 4) Behind the detached retina there are pigment helium membranes and old haemorrhages Ciliary epithelial proliferation and a ounced Ringschwiele are noticed Iron stain is positive in the retina and lens helium Alcian blue Colloidal iron and P A S stainings reveal no abnormal saminoglycans in the cornea or sclera when compared with two other eyes children with primary hyperplastic persistent vitreous Murexid staining for am is negative *No fungi or bacteria in special stainings Transversal sections of* disc and the atrophic optic nerve reveal normal central vessels without thrombi

Comments

high excretion of galactose in the urine and the very elevated galactose 1 phate of the erythrocytes together with the very decreased concentration of rocytic galactose 1 phosphate-uridyl transferase confirm the diagnosis heredi galactosaemia The treatment resulted in regression of symptoms In galacto- ia, a few days after birth galactose 1 phosphate accumulates in the lens and metabolism becomes disturbed Untreated the disease results in cataract al retardation and hepatic damage followed by cirrhosis In minor galactosea cataract can be the only clinical manifestation (Christini 1957 Torselli & lena 1960) In a single case of galactosaemia cataract has been demonstrated ectron microscopy in a five month old fetus (Vannas et al 1975) At the age of 7 weeks the cataract often appears as a ring resembling a drop of oil in the e of the lens (Nordmann 1966) About 2 weeks later it begins to spread into al vacuoles and progresses to complete opacification of the lens

e literature from 1908-53 has been summarized by Patz, who found cataract as nly ophthalmological complication to galactosaemia Wilson & Donnel (1958) d eight cataracts in 12 patients with galactosaemia but no other ophthalmologi omplications Hsia & Walker (1961) found two cases of galactosaemia with ocular haemorrhages *and detachment of retina in one case resulting in* lness

o my knowledge a persistent hyaloid artery has not previously been discribed in ection with galactosaemia

our case there are two possible explanations 1) A persistent arteria hyaloidea m with large *intraocular haemorrhages after birth 2) Intraocular haemorrha* before or during the 7th embryonal month causing persistence of the hyaloid ery

The first possibility fits well with the ultrasonic findings and seems the probable in this case

An interesting finding in this case is that the persistent hyaloid artery anas ses with an artery in the ciliary body and the episclera

Some foci of extramedullary haemopoiesis seen in the retina are also discovery The hemopoietical tissue of mesodermal origin is normally seen the vascular plexes around the optic cup (Barber 1955)

A rupture of these vessels followed by migration of the cells towards the may explain this finding

Follow up April 1980

The boy is still on galactose free diet, and his condition and visual acui improved

The boy is now able to collect small balls from the floor and follows with subjects with the remaining eye

There is still an undulatory nystagmus slight zonular cataract and posterior polar cataract

References

Barber A N (1955) Embryology of the Human Eye p 44–50 181–182 Mosby St I

Brandt N J (1966) Galactose-1 P Uridyl Transferase *Thesis* p 18? Munksgaard hagen

Hsia D Y Y & Walker F A (1961) Variability in the clinical manifestations of galac *J Pediat 59* 872–883

Nordmann J (1966) Early postnatal cataract *Amer J Ophthal 61* 1253–1263

Patz A (1953) Cataract in galactosaemia. *Amer J Ophthal* 36 453

Vannas A Hogan M J Globus M S & Wood I (1975) *Lens changes in a galactose Amer J Ophthal 80* 726–733

Wilson W A & Donnell G N (1958) *Cataract in galactosaemia Arch. Ophthal* Ch 215–222

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ADVANCED RETINOBLASTOMA IN MALAYSIAN CHILDREN

BY

D SINNIAH G NARASIMHA and K. PRATHAP

Twenty children with retinoblastoma are reviewed who were treated at the University Hospital Kuala Lumpur over a 10-year period They constitute 6 6% of childhood malignancies and without exception all presented with advanced disease Hereditary cases were notably absent in the the series probably because past cases have almost invariably succumbed without an opportunity to transmit the gene With enucleation and radiotherapy six of the patients have survived from 2 to 12 years The addition of vincristine and cyclophosphamide has not been associated with improved survival

Key words retinoblastoma – histological staging – therapy – survival

noblastoma the commonest intraocular tumour in childhood occurs either adically as a result of spontaneous mutation or as an inherited autosomal inant characteristic Its frequency varies from 1 in 15 000 to 1 in 30 000 live ns (Schappert Kimmijser et al 1966 Francois & Van Leuven 1964) An easing incidence has been recorded in recent years and this has been attributed mproved methods of treatment resulting in more survivors transmitting the etic defect and to an increase in the rate of spontaneous mutation (Bedford & amar 1975) The paucity of data from developing countries has prompted us to iew the epidemiological clinical and histopathological features the staging and response to treatment in children with retinoblastoma seen at the University spital, Kuala Lumpur over a ten year period as compared with those from other ntries.

eived January 8 1980

5*

Materials and Methods

All cases of retinoblastoma admitted to the Paediatric Unit during the period I through 1977 were studied Details of the illness family history investigat response to therapy and outcome were reviewed The tumours were st according to the scheme proposed by Reese & Ellsworth (1963) and modifie Bedford et al (1971) Since 1976 stage V and VI cases have received all 3 mod of treatment, namely surgery radiotherapy and chemotherapy The latter w vincristine 1 5 mg/M² IV plus cyclophosphamide 300 mg/M² IV once every w for one year Eyes enucleated as part of treatment were subjected to de histopathological review to confirm the diagnosis and staging and to stud relationship to prognosis

Results

Epidemiology

During the index period 20 children (9 males and 11 females) with retinobl were admitted and they account for 6 6% of all childhood malignancies comprised 13 Chinese 4 Malays and 3 Indians who reflect the racial compos patients admitted to the Unit. Their mean age at presentation was 30 7 month ranged from 8 months to 7 years 14 were aged less than 3 years Unlike other (Bedford et al 1971) there was no family history of retinoblastoma altho children presented with bilateral disease

Clinical Features

The mean duration of symptoms prior to diagnosis was 8 4 months and r from 3 days to 30 months The commonest symptoms at the time of diagnos white pupil reflex loss of vision and swollen painful red eye None of the p complained of squint as seen in Table I

The tumour originated in the right eye in 13 cases the left eye in 3 bilaterally in 3 cases and was unrecorded in 1 case respectively Six childr

Table I

Clinical features of 20 cases of retinoblastoma

Presenting Symptoms	No of cases
White pupil reflex	17
Loss of vision	5
Swollen painful red eye	3
One pupil bigger than the other	1
Squint	0

e V disease 12 had stage VI disease and in 2 patients the stage was not
orded

he VMA screening test was positive in 5 of 8 cases Chest X ray and skeletal
ey revealed orbital calcification in 3 cases with blurring of the orbital margin in
instance Cerebrospinal fluid yielded malignant cells in 2 cases and evidence of
ulent meningitis in another

tment and Outcome

ost all the patients presented with either stage V or VI disease Their
ological features treatment and outcome are recorded in Table II Two
nts refused treatment while the rest had enucleation of the affected eye Of
e patients who had only enucleation done 2 were lost to follow up one died of
-operative meningitis while 2 others are tumour free 4 and 6 years after
ery respectively Ten patients received post-operative radiotherapy and of
e 5 have survived from 2 to 10 years without tumour recurrence 3 were lost to
w up and 2 developed widespread metastases

hree patients with stage VI disease received all three modalities of treatment
ely surgery radiotherapy and chemotherapy One patient (case No 16)
loped CNS infiltration with cerebrospinal fluid involvement and was success
treated with intrathecal methotrexate and systemic vincristine adriamycin and
ophosphamide (VAC) but was lost to follow up The other 2 (cases No 17 and
suffered from re-emergence of tumour whilst receiving continuation
notherapy and of these one was lost to follow up while the other succumbed to
astases despite intrathecal methotrexate and systemic (VAC) therapy

Discussion

erto no studies on retinoblastoma have emerged from this part of the world Its
incidence has not been established in Malaysia but it accounts for 6 6% of all
gnancies in childhood seen at our centre compared with 3% in the United
gdom (Lawson & Steward 1975) The absence of sexual bias supports an
osomal mode of transmission The mean age of our patients higher than that of
dren reviewed by Bedford et al (1971) and Kock & Naeser (1979) is probably
ted to late presentation with more advanced disease and the apparent absence
hereditary cases in our series Francois et al (1964) have found that non
editary cases have a higher mean age at diagnosis than hereditary cases A family
ory of retinoblastoma appears to be rare in Swedish reports (Jereb et al 1967
ndal et al 1973) and supports the suggestion that most cases of retinoblastoma
sporadic (Duke Elder 1967) The absence of a family history in our series is
bably because our earlier cases have invariably succumbed to the disease without

Table II

Clinical Details Treatment and Outcome in 20 cases of Retinoblastoma

Case No	Year	Age at Diagnosis	Sex	Pathological Findings	Staging of Disease	Treatment			Outcome
						Surgery	Surgery & R T	Surgery + R T + Chemotherapy	
1	1968	7 years	F	ONI	VI	–	+	–	*Bone metastases at 13 months – went* abroad
2	1968	2 years	F	ONI	VI	–	+	–	A + W *10 years later*
3	1969	2 years	F	*date not available*	?	–	+	–	A + W 12 years later
4	1970	10 months	M	corneal tags (L) (R) scattered creamy patches opaque media	V (bilateral)	0	0	0	Refused treatment
5	1970	13 months	M	tumour involving half the retina	V	+	–	–	A + W 13 months later Lost to F U
6	1971	8 months	M	data not available	? (bilateral)	0	0	0	Refused treatment
7	1971	18 months	F	t m ur in [illegible] half the etina	V	–	+	–	A + W 2[illegible] m [illegible] l te [illegible] to F U
8	197[illegible]	27 [illegible]	M	ex [illegible] extension [illegible] a [illegible] ONI	VI	–	+	–	A + W [illegible]
[illegible]	197[illegible]	[illegible]	F	[illegible]	VI	[illegible]	–	–	Al[illegible]

				V ONI					[illegible]
12	1971	30 [illegible]	F	ONI	VI	–	+	–	A + W [illegible] lost to F U
13	1974	3 years	F	anterior & posterior chamber	VI	+	–	–	A + W 1 years
14	1975	20 months	M	ONI	VI	–	+	–	Died within 5 weeks of cerebral & spinal metastases
15	1975	26 months	M	vitreous seeding	V	–	+	–	A + W at 2 years 9 months
16	1976	4 years	F	ONI	VI	–	–	+	CNS involvement at 5 months responded to R T MTX and VAC Lost to F U
17	1976	22 months	M	ONI	VI	–	–	+	tumour in opposite eye at 7 months Sent for R T Lost to F U
18	1976	7 years	F	ONI	VI	–	–	+	CNS involvement at 1 years No response to MTX VCR ADM and CTX Died 3 weeks later
19	1976	11 months	F	ONI	VI	–	+	–	Lost to F U at 2 months
20	1977	8 months	F	(Right) ONI (Left) stage V	VI (bilateral)		+	–	Lost to F U at 1 month

ONI = optic nerve infiltration A + W = alive and well F U = follow up R T = radiotherapy MTX = methotrexate
VCR = vincristine CTX = cyclophosphamide ADM = adriamycin

an opportunity to reproduce and *transmit* the gene to their children. The side location of the tumour reveals an even greater preference for the right compared with similar reports from the Scandinavian countries (Kock & Naeser 1979). The reason for this is not clear

Our experience with the treatment of retinoblastoma has been confined to advanced disease. Eight of *our 20 children* have survived more than one year and for periods ranging from 2 to 12 years. Our cure rate compares favourably with the 29 36% rate reported by Ellsworth (1977). The addition to *chemotherapy* did *not* appear to have improved survival and the appearance of tumour during maintenance chemotherapy in 2 cases suggests that the combination used by us is ineffective. It would be more rational to use methotrexate BCNU CCNU or DTIC which cross the blood brain barrier but this would need evaluation. The effective treatment currently available for advanced disease appears to be enucleation *followed* by *orbital* radiotherapy. The presence of tumour cells in the anterior chamber or infiltration of tumour into the optic nerve is not necessarily equated with poor prognosis (Kock & Naeser 1979)

References

Bedford M A Bedotto C & Macfaul P A (1971) Retinoblastoma – a study of 139 cases *Br J Ophthal 55* 19–27

Bedford M A & Freeman J E (1975) Retinoblastoma In Cancer in Children pp 1[illegible] Springer Verlag Berlin Heidelberg New York

Duke Elder S (1967) System of Ophthalmology Vol X pp 678

Ellsworth R M (1977) Retinoblastoma *Med Probl Ophthal 18* 94–100

François J & Matton van Leuven M T (1964) Recent data on the heredity of retinoblastoma In Ocular and adnexal tumours pp 123 C V Mosby Co St Louis

Jereb B Kock E & Asard P E (1967) Prognosis of retinoblastoma treated at Radiumhemmet *1926-1963 Acta Radiol (Stockh) 6* 369–377

Jerndal T Lindstedt E Svensson T & Akerskog G (1973) Retinoblastoma in Sweden. A study of 45 children with retinoblastoma with special regard to the therapeutical result *Acta ophthal (Kbh) 51* 543–550

Kock E & Naeser P (1979) Retinoblastoma in Sweden 1958 1971 A clinical and histological study *Acta ophthal (Kbh) 57* 344–350

Lawson D N & Steward J K (1975) Facilities for paediatric cancer cases and childhood tumour registration In Cancer in *Children pp* 85 89 Springer Verlag Berlin Heidelberg New York

Reese A B & Ellsworth R M (1963) The evaluation and current concept of retinoblastoma therapy *Trans Amer Acad Ophthal Otolaryng 67* 164–1[illegible]9

Schappert Kimmijser J Hemmes G D & Nijland R (1966) The heredity of retinoblastoma *Ophthalmologica 151* 197–213

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BER S MILIARY ANEURYSM AND DYSBETALIPOPROTEINAEMIA
A Case Report

BY

VICTOR GODEL LUCIAN REGENBOGEN and MOSHE LAZAR

A 19-year-old male suffering from Leber s miliary aneurysm was also found to be affected by a dysbetalipoproteinaemia (type IV hyperlipoproteinaemia) The pathophysiologic mechanism of the condition and the possible metabolic cause are discussed In view of such findings evaluation of plasma lipids in patients with Leber s miliary aneurysm would seem to be warranted

Key words dysbetalipoproteinaemia – fluorescein angiography – Leber s miliary aneurysm

ce Leber described the disease of miliary aneurysm (Leber 1912) several other ts have been recorded and evidence has been forthcoming which conveys a tionship between this retinal condition and certain associated systemic disorders r reasons which are unexplained the condition appears in young males and is tally unilateral Many possible causes for Leber s miliary aneurysm have been posed but there is no conclusive evidence for any of them

t is the purpose of this presentation to describe a patient with Leber s miliary eurysm not only as an addition to the literature but also as a report on an ociated metabolic defect which does not appear to have been previously ntioned

ceived October 31 1979

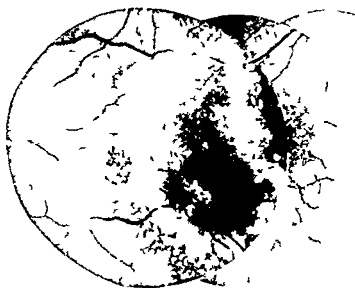


Fig 1
The fundus of the right eye with the bulb-like dilatations of the infero temporal a... the circinate lesion with exudative rings involving the macula.

Case Report

This 19 year-old male was referred to us because of a gradual visual acuity deterioration... his right eye He had been well until the time that he complained of visual problems ... interferred with his studies He did not complain about any other disease his past history... essentially negative and a detailed family history showed no evidence of any systemic...

When examined vision in the right eye was 20 80 and in the left 20 20 The intraoc... pressure and the anterior segment were normal Abnormal findings were confined to the right fundus These abnormalities included a patch of fatty exudation deposited in a c... fashion (Fig 1) These hard exudates surrounded some aneurysmal dilatations distal t... 2nd and 3rd bifurcation of the inferior temporal artery These vascular disorders were f... only along divisions of the inferotemporal artery the veins remaining normal in appear... The walls of the involved arteries were thickened and whitish in the region of these sac... dilatations A limiting fibrous layer with mild retinal oedema circumscribed the sac... aneurysms The dense ring of fatty degeneration crossed the macular region expl... fall in visual acuity The retinal arterial tree demonstrated an increased light reflex. The lumen of the inferior temporal artery presented regional narrowing of its calibre Biomic... scopic examinations revealed the presence of telangiectatic dilatations of the fine ... capillary bed adjacent to the circinate area



Fig 2

kcein angiography of the right eye Left Early arterio-venous phase demonstrating in perfusion of the infero temporal artery and its orresponding capillary bed ting for the hypofluorescent patch Middle Arterio- enous phase showing telangiecta tations of the precapillary arterioles and capillary bed Right Late phase showing cular leakage of dye evidenced by the development of stainir g urrounding the areas of aneurysms and telangiectatic vessels

al field demonstrated a scotoma in the right eye without break through nto the ery and corresponding to the diseased area Colour testing ga e a defect n the blue axis for the right eye but normal response in the left Dark adaptation for cone id thresholds slightly elevated in the right eye was n rmal in the left The retinogram presented subnormal amplitudes in the right eye However both the pic and scotopic components were present.

rescein angiography demonstrated arteries with segmental narrowing and saccular ion al ng the inferior temporal branches In the early arterial phase fluorescein was ed by these aneurysmal lesions their diameters being twice that of the involved s The transit of the dye was normal to the site of the aneurysm but presented marked of filling of the artery distally to it (Fig 2 left) Furthermore the aneurysm acquired a essive dense fluorescence and a zone of intraretinal leak was found in the area diately surrounding this The capillary network was isible and dilated The branches of twork was visible and dilated The appearance of multiple hyperfluorescent spots with ts corresponding to the telangietatic lesions noted on ophthalmoscopy confirmed the nce of vessels studded with microaneurysms (Fig 2 middle) In the late venous phase of iogram (Fig 2 right) a d ffuse and dense staining was seen indicating extensi e dye

leakage from the capillaries and microaneurysms The vessel wall stained ... the point of the aneurysms retaining the dye longer than the underlying vessels. The area of dye leakage was much more widespread than could be appreciated from the ophthalmoscopic changes

Since many different causes can initiate the clinical picture of intraretinal and ... exudation detailed investigations were performed in an attempt to correlate ... laboratory changes with this retinal condition The standard laboratory tests includ... plasma cholesterol yielded normal findings However the patient's triglycerides were ... to 250 mg/dl As such a plasma lipid disturbance was found further studies with lipo... electrophoresis were carried out to fully define the abnormality A dense pre-beta band ... lipoprotein electrophoresis was obtained and on the basis of the elevated plasma ... des with normal plasma cholesterol the diagnosis of type IV hyperlipoproteinaemia ... established As this type of lipoprotein abnormality with hypertriglyceridaemia is known ... carbohydrate induced a low carbohydrate diet was initiated since there is little else ... be done Photocoagulation treatment of the retinal lesions was in the meantime withheld

Discussion

The pattern of the retinal anomaly in our patient was specific enough to su... Leber's miliary aneurysm

The pathophysiological mechanism underlying this anomaly is not clear alth... there are some suggestive observations in patients who have had asso... involvements of other parts of the body The occurrence of such combined ... would appear to establish the point of view that the disease process in not ... ocular

The frequency of unilateral involvement and the absence of any hereditary ... lent credence to the belief that Leber's miliary aneurysm is due to a developm... anomaly occurring as an isolated aberration of retinal vasculature (M... Wegener 1969) However simultaneous instances of telangiectasis in the retina ... elsewhere in the vascular system were supported by the occurrence of aneur... lesions in the retina and capillary disorders in the nasal mucous membrane (Gu... & Draf 1975) Evidence for such a nature of the causative lesion was also sug... by a patient with Leber's miliary aneurysm in the left eye and optic atrophy ... right eye (Archer & Krill 1971) In this case assumptions were brought forth ... common cause of both conditions with telangiectatic peripheral retinal vess... one eye and retrolbulbar telangiectasis of the nerve head in the other Sc... patients have been described with involvements of other parts of the body ... relationships to systemic disorders such as epilepsy (Bryson & Wolter ... phakomatosis (Paufique et al 1964) or Osler's disease (Heffrer & Schuster ... were documented

n other cases the clinical features associated with Leber s miliary aneurysm were h that the possibility of a metabolic factor could be born in mind In our case abolic defect of dysbetalipoproteinaemia type was also found Assuming Leber s ary aneurysm is the result of such a metabolic disturbance it is conceivable that ertriglyceridaemia per se is not the only etiologic factor Hyperproteinaemia han et al. 1964) globulins or particular globulins fractions (Kahan et al 1964) ogamaglobulinaemia (Frenkel & Russe 1967) and hyperlipaemia with hyper lesterolaemia (Kahan et al 1964) were thought to be equally important in the esis of this disease Our patient represents an example of a case with normo-lesterolaemia associated with abnormal lipoprotein structure but without excess ulating cholesterol The primary defect appeared to be the occurrence of ormal beta lipoproteins which contained an excess of triglycerides Considering finding from the wider perspective of plasma lipoprotein disturbance rather n the more limited consideration of triglyceridaemia, it is apparent that such abolic dysfunctions may be added to the etiology of Leber s miliary aneurysm

he pathophysiologic mechanism by which the retinal changes are produced has ained elusive It has been thought (Houston & Wise 1957) after consideration heir characteristic pattern in circinate retinopathy that these exudates were due multiple zones of retinal hypoxia secondary to local vascular obstruction ether this fatty material arises from dilated capillaries adjacent to hypoxic retinal as or whether it represents a by product of the altered metabolism which have ed from the capillaries and cannot be resorbed is not known

The flourescein angiography was helpful in detecting and defining the structural l the permeability changes in the affected vessels and in demonstrating the ent of the extravascular leakage The angiography demonstrated not nl the inal artery involvement but also the fine capillary bed alteration The e ted illary bed showed diffuse as well as focal dilatations which ere ma nt hthalmoscopically

t seems that the etiopathogenesis of Leber s miliary aneurysm cannot be duced from present information nor is it clear whether any correlation between ir appearance and any systemic disease exists apart from speculation that they n both be due to the same basic abnormality The possibility that the hypertri ceridaemia in our patient may be fortuitous rather than causative or that both retinal disease and the dysbetalipoproteinaemia may be a reflection of a causally related metabolic defect cannot be excluded

The true physiological significance of such a metabolic defect remainas to be ermined and warrants further investigation Additional cases are needed to firm and possibly extend the above observation

Acknowledgment

We are indebted to Dr E Baruch for his valuable help and to Mr A Sher for [illegible]
evaluation

References

Archer D & Krill A E (1971) Leber s miliary aneurysm and optic atrophy [illegible]
384–400

Bryson J M & Wolter J R (1966) Leber s miliary aneurysm with central nervous
dysfunction *J Pediat Ophthal 3* 26–27

Frenkel M & Russe H P (1967) Retinal telangiectasia associated with hypogammaglob-
emia *Amer J Ophthal 63* 215–220

Gartner J & Draf W (1975) Leber s milliary aneurysms associated with telangiectasia
nasal mucosa *Amer J Ophthal 79* 56–58

Heffner R R & Solitaire G B (1969) Hereditary haemorrhagic telangiectasia neuro-
logical observations *J Neurol Neurosurg Psychiatr 32* 604–608

Houston W R & Wise G N (1957) Circinate retinopathy *Arch Ophthal (Chic*
777–783

Kahan A Kahan I L & Piritsi K (1964) Humorale Ursache der Miliaraneurismen-R
(Leber) *Klin Mbl Augenheilk 144* 361–370

Leber T (1912) Uber eine durch Vorkommen multipler Miliar aneurysmen charakter
Form von Retinaldegeneration *Arch Ophthal 81* 1–14

Maggi C (1963) Leber s retinal degeneration with miliary aneurysms *Amer J Oph*
901–907

Paufique L Ravault M P Bonnet M & Istre M (1964) L angiomatose miliaire retinie
Leber *Ann Oculist 197* 937–955

Wegener J K (1969) Leber s retinal degeneration with miliary aneurysms *Acta O*
(Kbh) 47 108–114

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CASE OF MESENCHYMAL CHONDROSARCOMA OF THE ORBIT

BY

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and TERUMASA SASHIKATA[2]

A case of mesenchymal chondrosarcoma occurring in the right orbit of a 84-year-old Japanese female was reported The ultrastructural findings of tumour are composed of three cell types well-differentiated cartilaginous cells undifferentiated cells and transitional cells The well-differentiated cells showed scalloped cytoplasmic membranes numerous mitochondria showing dense electron matrix various size of lipid granules and abundant amount of extracellular matrix. The extracellular matrix were collagen fibres and ground substances and matrix vesicle The undifferentiated cells showed smooth cytoplasmic membranes large nuclei resembling primitive mesenchymal cells

Key words 84 year-old patient – orbital mesenchymal chondrosarcoma – undifferentiated – transitional – cartilaginous

-senchymal chondrosarcoma is a rare tumour which has been described originally Lichtenstein & Bernstein (1956) It is generally accepted that 70% of the cases -e occurred in bone and the remaining 30% have originated from soft tissues To -r knowledge only 12 orbital mesenchymal chondrosarcoma (Dabrowska 1972 -ction et al 1973 Mizuno et al 1978 Okuda et al 1976 Ramirez et al 1971

-ved December 8 1979

Reeh 1966 Salvador et al 1971 Sevel 1974 Silva et al 1977 Zielinska & C 1977) have been reported Until recently however electron microscopic tion of the tumour was not described in all of the reported cases except report In the present paper the author describes the light and electron mic findings in a case of a 84 year-old Japanese female with orbital mesen chondrosarcoma

Case Report

A 84 year-old woman was admitted to Hyogo College of Medicine Hospital on O 1977 complaining of a 3 year history of gradual proptosis with swelling of the lids right eye (Fig 1)

A firm smooth surfaced tumour pushed the right eye laterally and upward exophthalmometer right 20 mm left 14 mm) and the eye movement was severely

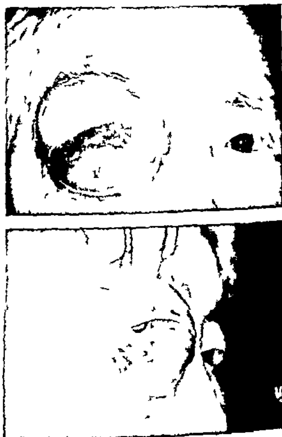


Fig 1
Exophthalmos and eversion of the inferior fornix due to the orbital tumour

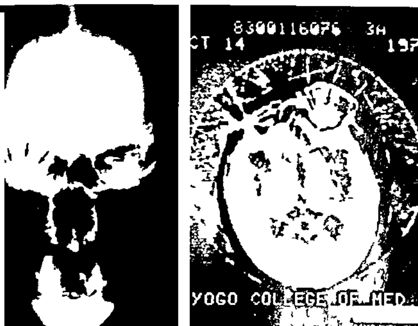


Fig 2
radiodense opacity in the right orbit. High and low den it in the right orbit by CT scan

directions The vision of the right eye was already lo t. Roentogenogram examination d a brai like high radiodense opacity in the right orbit CT scan also showed two ns of high and low density in the same region (Fig 2) The tumour a extirpated on er l 19/7

ss findings The extirpated tumour was 5×5×3 cm in size and about 42 g in weight. Cut surfaces revealed brownish white elastic hard mass with foci of ication and grayish white semi translucent nodules

ods for h stological investigation

tissue for light microscopy was fixed in 10% formalin processed sectioned as ntional method and tained with haematoxylin and eosin and other sta nings such as alcian blue and silver impregnation

electron microscopic observations approximately 1 mm thick blocks were fixed in 1% im tetroxide in phosphate buffer (pH 7 4) dehydrated in alchol and embedded in Epon 1 µ semithin sections were stained with toluidine blue and ultrathin sections were doubly with uranyl acetate and lead nitrated and were examined with Akashi S-500 electron scope.

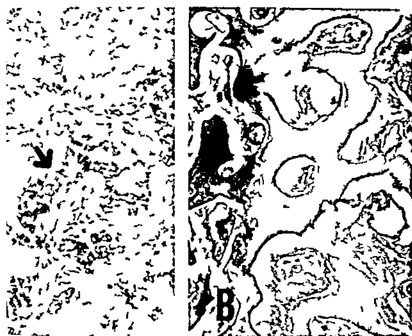
Fig. 3 A B

A Undifferentiated cellular area H. E. × 140

B Vascular pattern resembling haemangiopericytoma. H. E. × 140

Fig. 4

Higher magnification of a cartilaginous island. Alcian blue staining × [illegible]



F g 5 A B

A Calcificat on in the center of the cartilaginous sland H E ×
B Ma ure bone formation in the peripheral part of the tum u H E 140

op c f nd ngs

mour showed two types of h stology Most of the tumour was composed of mall o oid or short sp ndle shaped cells w th scanty cytoplasm and centrall located Large These tumour cells were often found to arrange around the abundant cap llar ls, resembling the pattern seen in haemangiopericytoma (F g 3)
ng these cellular areas there were cartilaginous slands of various s ze with somewhat d chondrocytes showing moderate nuclear atyp sm but rare m tosis (F g 4) In certain alcificat on was found in the center of the cartilaginous slands At the peripheral part umour adjacent to the orb t mature bone formation was also found (F g 5)

ructural f nd ngs

erentiated cellular area cons sted of round or oval cells ha ng large round or ovo d F g 6) The plasma membrane was smooth The m tochondria were round n shape cytoplasmic organellae such as rough endoplasm c ret culum and free ribosomes were Lipid droplets were not present in these und fferen iated cells Most of the round or lls were arranged close to each other and the nter-cellular matrix was sparse
epresenting trans t onal or ntermed ate forms between und fferentiated cells and rocytes were observed These cells showed elongated or stellate conf guration with



Fig 6
Undifferentiated cells showing scanty cytoplasma with a few mitochondria a endoplasmic reticulum × 24 150 bar = 1μ.

several coarse cytoplasmic processes (Fig 7) They were separated from each collagen fibers The characteristic findings of the cytoplasma were as follows the d mitochondrial matrix was higher than that of undifferentiated cells Furthermor cytoplasma vacuoles of various sizes were observed

Within the islands of well differentiated tumour cells typical features of chondroc seen (Fig 8) The cell membrane was characterized by a scalloped margin The nu ovoid with diffuse chromatin The cytoplasma contained lipid vacuoles of varying moderate number of mitochondria showing electron dense matrix and r u h endo reticulum Small particles which may be a staining product of lead compound e observed adjacent to the cell membrane

Discussion

The histological appearance of this tumour was considered distinctive It co of proliferation of primitive undifferentiated mesenchymal cells in which sca islands of well differentiated cartilage were present We found mature

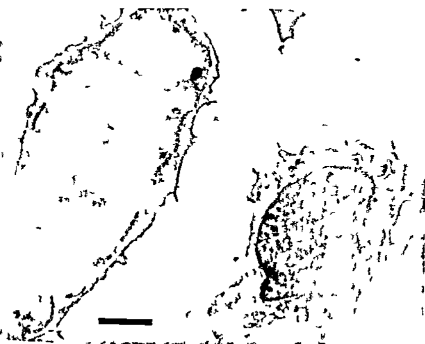


Fig 7

... representing transitional form with several coarse cytopla... ...nd mitochondria with denser matrix × 17 700 bar ...

...rmation in the peripheral area of the tumour Salvador et al (1... ...d... ...
...e findings We assumed that this bone formation was a result of
...e well-differentiated cartilaginous islands because of the long d... ...ati...
...mour

Mesenchymal chondrosarcoma closely resembles haemangiopericytom... ...reticu...
...m cell sarcoma fibrosarcoma and ordinary chondrosarcoma and it i... ...sometimes
...fficult to differentiate from them When the cartilaginous area is observed ... it i...
...er to differentiate from haemangiopericytoma and from reticulum cell sarcoma
...e cells of fibrosarcoma are larger than those of mesenchymal chondrosarcoma
...e cartilaginous cellular elements of ordinary chondrosarcoma are larger and
...ore pleomorphic than those of mesenchymal chondrosarcoma

Ultrastructural studies of the tumour were reported by several authors (Fu & Kay ...4 Mikata et al 1977 Mizuno et al 1978 Steiner et al 1973) Mizuno et al ...) have reported ultrastructural aspects of orbital mesenchymal chondrosar...oma, however the description was limited to the undifferentiated cellular area In the present case electron microscopic features have shown three types of tumour



Fig 8

Well differentiated chondrocytic form of tumour cell showing scalloping processes probably vacuoles (arrows) and pericellular matrix × 23 000 bar = 1μ.

cells undifferentiated cells transitional cells and cartilaginous cells Fig 9 sho scheme of relationship between these tumour cells As for the undifferenti cells the present observations are in agreement with those of previous rep However as for the transitional or cartilaginous type of tumour cells se different features were shown compared with those of Steiner (1973) or M (1977) report Namely in the present case mitochondria showing electron d matrix and various sizes of lipid droplets were found in almost all transitional cartilaginous cells

According to Hay (1978) and Jakobiec & Tannenbaum (1974) orbital mesen are classified in four groups primary secondary haemocytic and neuro mesenchym and secondary mesenchym are derived from both mesoderm neural crest Tumour orginated from the secondary mesenchym are fibrosarc osteosarcoma chondrosarcoma leiomyoma sarcoma haemangiopericytoma, rous histiocytoma and liposarcoma Therefore the origin of this case seems t secondary mesenchym though not definitely from mesoderm or from neural cr

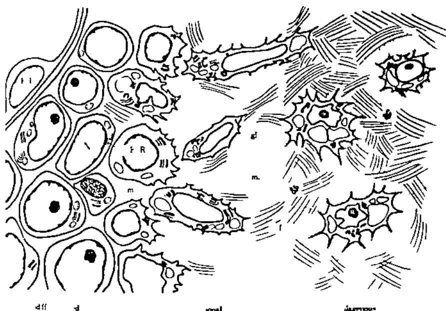


Fig 9

hema of the mesenchymal chondrosarcoma Cap Capillary End Endothelial cell N ucleus r E R rough Endoplasmic Reticulum mit mitochondria gly glycogen m v matrix vesicles c f collagen fiber

References

abrowska Z T (19?9) Mesenchymal chondrosarcoma *Arch Ophthal (Chicago) 8?* 85

S & Kay S (1974) A comparative ultrastructural study of mesenchymal chondrosarcoma and myxoid chondrosarcoma *Cancer 33* 1531–1542

uction J C Font R L Enzinger F M & Zimmerman L E (1973) Extraskeletal mesenchymal chondrosarcoma *Arch Path 95* 336–340

ay E D (1968) Organization and fine structure of epithelium and mesenchyme in the developing chick embryo In Fleischmajer L & Billingham R (Eds) Epithelial Mesenchymal Interactions pp 31–55 Williams & Wilkins Co Baltimore

akobiec F A & Tannenbaum M (1974) Embryological perspectives on the fine structure of orbital tumours *Int Ophth Clin 15* 85–110

ichtenstein L & Bernstein D (1959) Unusual benign and malignant chondroid tumours of bone. A survey of some mesenchymal cartilage tumours and malignant chondroblastic tumours including a few multicentric ones as well as many atypical benign chondroblastomas and chondromyxoid fibromas *Cancer 12* 1142–1157

Nata A Iri H & Inuyama Y (1977) Mesenchymal chondrosarcoma A case report with an ultrastructural study and reviews of Japanese literatures *Acta Path J p 27* 93–109

Mizuno K Yuasa T Sakiyma T & Kobayashi A (1978) A case of mesenchymal chondrosarcoma in the orbit (In Japanese) *Folia Ophth Jpn* 29 1036–1039
Okuda K Ouchi E Nakano K & Yanagida K (19 6) A case of mesenchymal chondrosarcoma of the orbit (in Japanese) *Folia Ophth Jpn* 27 557–560
Ramirez L C Saavedra J A & Buen S (1971) Mesenchymal chondrosarcoma of the orbit Report of the first case in orbital location *Arch Ophth (Chicag)* 86 410–413
Reeh M (1966) *Haemangiopericytoma with cartilaginous differentiation in the orbit Arch Ophth (Chicago)* 75 82–83
Salvador A H Beabout J W & Dahin D C (1971) Mesenchymal chondrosarcoma observations on 30 new cases *Cancer* 28 605–615
Sevel D (1974) Mesenchymal chondrosarcoma of the orbit *Brit J Ophth* 58 882 887
Silva E D T Filho M F Kuhn M L S & Andrade G E (19) Chondrosarcoma of the orbit A case report *A R Q Neuro-Psiquiat (San Paul)* 35 156–169
Steiner G C Mirra J M & Bullough I G (1973) Mesenchymal chondrosarcoma A study of the ultrastructure *Cancer* 32 926–939
Zielinska B B & Cyperling A (1977) Chondrosarcoma mesenchymal orbitae *Klin Oczna*
303–305

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UNUSUAL COURSE OF PAINFUL OPHTHALMOPLEGIA
REPORT OF A CASE

BY

BO I. ANDERSSON

A case of Tolosa-Hunt syndrome with unusual course is described. Pain and ophthalmoplegia were both relatively late manifestations preceded for several weeks by progressive involvement of the optic nerve. The importance of also bearing this condition in mind in atypical cases is stressed, since early diagnosis and corticosteroid treatment distinctly reduce the risk of severe residual symptoms.

Key words: Tolosa-Hunt syndrome – painful ophthalmoplegia – superior orbital fissure syndrome – oculomotor paralysis – cavernous sinus syndrome – orbital apex syndrome.

he symptom complex of painful ophthalmoplegia may be attributed to various auses amongst which the most important are carotid aneurysm, collagen disease, iabetes, neoplasms, specific granulomatous conditions and so far unspecified ammatory processes. The Tolosa-Hunt syndrome exemplifies an inflammatory ondition which is not well defined pathologically owing to the fact that only a few ccasional cases have been histologically examined (Tolosa 1954; Lakke 1962; chatz & Farmer 1972; Levy et al. 1975). Nevertheless, the disorder shows striking nd often uniform clinical features representing a clinical entity (Smith & Taxdal 1966). The prompt effect by corticosteroids upon in particular the pain has been

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emphasized (Smith & Taxdal 1966 Mathew & Chandy 1970 Hunt 19 6) This effect however is non specific and can only be used as a diagnostic criterion after thorough investigation (Fowler et al 1975)

All neurological structures in the region of the cavernous sinus the superior orbital fissure and the orbital apex may become involved to various extent and in any succession in the Tolosa Hunt syndrome However in the vast majority of reported cases pain and ophthalmoplegia were early symptoms and appeared in close connection with each other Notter s (1977) review disclosed only 5 out of 3 cases where pain was a late symptom or did not occur at all The optic nerve is rarely involved

The aim of the present case report is to call attention to this diagnosis even in cases where both pain and ophthalmoplegia are late manifestations

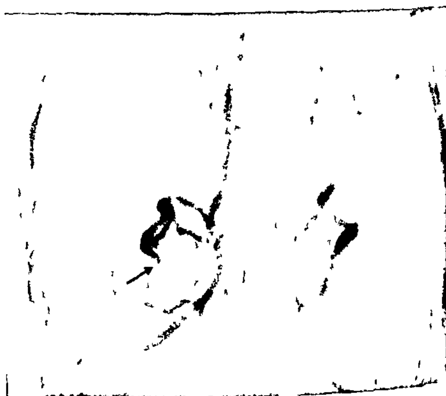


Fig 1

Orbital phlebography July 3 antero-posterior view No filling of the posterior part of right superior ophthalmic vein (arrow) and scant filling of the cavernous sinus on the same side



Fig 2
ıd angiography August 1 lateral view Slight local narrowing of the proximal intradural part of the carotid siphon (arrow)

Case Report

t is a 52 year-old man previously healthy and with no history of systemic or ie disorder In 19"6 he had a 3 week episode of pulsating pain around his right t objective neurological dysfunction In the middle of April 19/8 the patient fective colour vision The right central visual field was blurred and vision was aired with further progress during the following month In the beginning of May was examined by an ophthalmologist who found marked reduct on of visual) and a large central scotoma in the right visual field In the right fundus the optic ollen with peripapillary bleedings and slight segmental venous distension The the periphery were normal IOP was bilaterally normal The ESR was below 10 condition was interpreted as a central venous thrombosis From the middle of was progressive right sided retro-orbital pain intense and piercing in character later ptosis developed and oculomotor dysfunction due to involvement of the sixth nerves was noticed The ophthalmoplegia progressed as did the visual t, and at the end of June the right eye was amaurotic and there were total sixth external third nerve palsies Pain was unbearable and on ophthalmological n papilloedema of 6 to 7 dioptres ptosis and slight proptosis furthermore were

observed on the right side Treatment was given with 30 mg of prednisone daily Pain vanished within a couple of days and there was slight but temporary improvement of ptosis and oculomotor function An intraorbital expansive process was suspected, and orbital phlebography on July 3 disclosed obliteration of the posterior part of the right superior ophthalmic vein and of the right cavernous sinus (Fig 1) Roentgenographic examination of the skull and face were normal including orbital tomography A right carotid angiography on August 1 showed slight local narrowing of the proximal intradural part of the carotid siphon (Fig 2) An electroencephalogram was normal Inspection of the epipharynx was negative as were serology for lues and immunological screening including antinuclear factor On August 3 the ESR was 44 mm/h The steroid treatment was discontinued in the beginning of September and only a few days later pain recurred

On October 23 the patient was admitted to the neurological clinic Examination revealed total amaurosis and complete third and sixth nerve palsies on the right side Ptosis was total. The fourth and fifth nerves were normal There was atrophy of the right optic disc and the right pupil now was of intermediate size reacting neither directly nor consensually to light The ESR was 58 mm/h but routine laboratory examinations otherwise were normal including



Fig 3
Right carotid angiography October 31 lateral view The local carotid narrowing is now slightly more accentuated

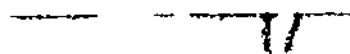




Fig 4
tal phlebography November 6 antero-posterior view Somewhat better filling of the posterior orbital collaterals on the right side otherwise unchanged

d glucose On suspicion of Tolosa Hunt syndrome corticosteroid treatment was again nued with 3 mg of prednisone daily Five hours later the patient was free of pain The owing month oculomotor function was partly restored and ptosis was completely ued, but amaurosis remained Angiographies were repeated and right carotid angiophy on October 31 showed some progress of the local narrowing of the carotid siphon ; 3) whereas orbital phlebography on November 6 principally was unaltered (Fig 4) nical course and ESR development are illustrated in Fig 5

n November 13 the patient developed massive bilateral pulmonary emoblism the source ng a clinically silent deep venous thrombosis of the right leg Treatment was given with arin and warfarin sodium but the latter was discontinued because of a gastric haemorr e. The question was arisen whether these complications were expressions of a generalized ebitis-vasculitis However this was not verified and a right temporal artery biopsy was rmal (undertaken during steroid treatment) as was coagulation status (antithrombin III) ttempts to withdraw steroid treatment resulted in a rise of ESR indicating a persisting ity of the inflammatory retro-orbital process The patient was discharged on December

Dornan T L Esp r M L E Gale E A M Ta tersall R B & Worth ngton B S 19 n Rem ttent pa nful ophthalmoplegia the Tolosa Hunt syndrome J Neu ol Neu g Psychiat 42 2 0 975

Fow ler T J Earl C J McAll ster V L & McDonald W I (19 5) Tolosa Hunt ndrome The dangers of an eponym Brit J Ophthal 59 149 154

Hunt W E Meagher J N LeFever H E & Zeman W (1961) Pa nful ophthalmoplegia Its relation to indolent inflammation of the ca ernous s nus Neu ology (M nneap) II 56 62

Hunt W E (1976) Tolosa Hunt Syndrome one cause of pa nful ophthalmoplegia J Neurosurg 44 544–549

Lakke J P W F (1962) Superior orb tal fissure syndrome Report of a case caused by local pachymen ngitis Arch Neurol Psychiat (Chicago) 289–300

Lenzi G L & Fieschi C (1977) Superior orb tal fissure syndrome Re ew of 130 cases Eu Neurol 16 23–30

Levy I S Wright J E & Lloyd G A S (1975) Orb tal and retro-orbital pseudotumour Mod Probl Ophthal 14 364–367

Lloyd G A S (1979) The local zat on of les ons n the o bital apex and ca ernous s nus by frontal venography Brit J Rad ol 45 405 414

Mathew N T & Chandy J (1970) Painful ophthalmoplegia J Neu ol S i II 243 256

M lstein B A & Morretin L B (1971) Report of a case of spheno d fissu e s ndrome studied by orb tal venography Amer J Ophthal 72 600 603

Muhletaler C A & Gerlock Jr A J (1979) Orb tal venography n pa nful ophthalmoplegia (Tolosa Hunt syndrome) Amer J Rad ol 133 31 34

Notter O (1977) Das Tolosa Hunt Syndrom Fort chr Neu ol Psychiat 44 4 9 440

Roman Campos G & Edwards K R (1979) Pa nful Ophthalmoplegia oculomotor nerve palsy w thout mydr as s due to compress on by aneurysm Headache 19 43 46

Schatz N J & Farmer P (1979) Tolosa Hunt Syndrome the Pa hology of Pa nful Ophthalmoplegia Neuro Ophthalmology pp 102 112 Mosby St Lou s

Smith J L & Taxdal D S R (1966) Painful ophthalmoplegia The Tolosa Hun s ndrome Amer J Ophthal 61 1466 1472

Sondheimer F K & Knapp J (1973) Angiograph c f nd ngs n the Tolosa Hunt s ndrome pa nful ophthalmoplegia Rad ology 106 105 112

Takeoka T Gotoh F Fukuuch Y & Inagak Y (1978) Tolosa Hunt syndrome Arteriograph c ev dence of mprovement n carotid narrow ng Arch Neu l 35 219 223

Tolosa E (1954) Periarteritic les ons of the carotid s phon w th the clinical features of carotid infracl no dal aneurysm J Neurol Neu o g Psy hiat 17 300–302

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Short Communication

SNAKE LIKE APPEARANCE OF NUCLEAR CHROMATIN IN CONJUNCTIVAL EPITHELIAL CELLS FROM PATIENTS WITH KERATOCONJUNCTIVITIS SICCA

BY

KIRSTEN MARNER

M ll pore f lter mprints of conjunctiva in pat ents w th conjunctival symptoms re ealed a snake l ke appearance of the chromatin in nuclei of ep thelial cells A total of 40 pat ents were in estigated Abnormal cells were found n 8 16 pa ents w th long term keratoconjunct v us s cca and n 6 24 pat ents sus pec ed for Sjøgrens syndrome The abnormal cells were typ cally arranged n clusters among morphologically normal ep thel al cells The find ng was s gn f cantly correlated to the severity of the d sease n patients with keratocon juncti us s cca In all pat ents the abnormal cells could only be detected in m pore mprints of the upper bulbar conjunct a and not n scrap ngs from the same area The s gn f cance of the find ngs are d scussed

Key wo ds keratoconjunct v t s s cca Sjøgren s syndrome nuclear chromat n conjunct al ep thel al cells

e use of mill pore filters has recently been introduced in ophthalmology as a face b opsy (Egbert et al 1977) The method is cla med to be simple gentle and eported to give a representative harvest of cells

Patients with keratoconjunctivitis sicca have dry and tender eyes and a conjunc

eived June 16 1980

tival biopsy is therefore painful and may be complicated As the millipore impr technique was found to be easy it was applied on the conjunctiva of keratoconjunc tivitis sicca patients

Material and Methods

Thirty five normal persons (70 eyes) were used as controls Sixteen patients (! eyes) with various degrees of keratoconjunctivitis sicca were examined 4–1 times monthly intervals Twenty four patients (48 eyes) with collagen disease we examined once for the diagnosis of Sjøgren s syndrome All patients and contr were investigated with Schirmer s test (basal secretion a m Jones 1966) break time (BUT) (Norn 1974) rose bengal staining (Norn 1977) and the millipo imprint technique Conjunctival scrapings were performed with a platinum spa and stained as described for millipore filters

Millipore filters (MF) type VS with pore size of 0 025 μm were used. In order remove water soluble surfactants from the pores of the filters they were soaked cold water for 30 min and air dried The filters were cut into 3 mm round pe and placed on a plastic (PVC) rod by use of double sided adhesive tape T mounted filter was pressed against the bulbar conjunctiva with a pressure of 25 mmHg for two seconds removed and fixed by Pro-Fixx® (Aerosol Cytol Fixative) or only air dried To achieve the constant pressure the plastic rod with filter was mounted on a tensiometer (Correx Haag Streit A G) The proced e performed with and without topical anaesthesia (oxibuprocaine Novesin® 0' with the same results When dry the filter was stained with PAS (periodic Schiff) and Mayer s hematoxylin After staining the filters were placed on a sli room temperature and air dried (one hour) cleared with xylol and coverslip before light microscopy In six cases the changes found in the chromatin pa were further investigated by Feulgen s nucleal test

Statistical analysis of the results was carried out using the Mann Whitney sum test

Results

During investigations performed to evaluate morphological differences of e lial cells in various areas of the eye nuclear changes were surprisingly fou some cells by use of the millipore filters However these changes possibly art conditioned by millipore filters showed certain localisation characteristics and restricted to certain patients

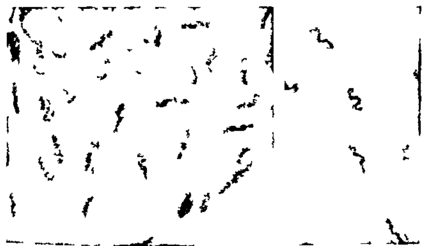


Fig 1

...eral stages from normal cells to straight line and snake like appearance of the chromatin in nuclei of the epithelial cells of the conjunctiva

Fig 2

...aracteristical snake like appearance of epithelial chromatin from a patient with severe keratoconjunctivitis sicca.

...ch figures are stained with periodic acid Schiff and hematoxylin (Magnification 1200 ×)

The nuclear changes in epithelial cells are illustrated in Figs 1 and 2 The nuclear ...omatin seemed to be condensed in a metaphase like pattern although the ...clear membrane was clearly visible Furthermore the picture was fairly homo...ous showing no prometaphases or anaphases However various intermediates ...re seen between a straight axial and a "snake like" appearance in different ...tients In one patient there was a predominance of one type By use of ...A-staining (Feulgen s nucleal test) it was secured that all DNA was contained in ...e described configurations

These abnormal epithelial cells were characteristically clustered and the clusters ...nstituted a few cells to more than 50% of all cells The imprints containing these ...normal cells were always from the upper bulbar conjunctiva. Until now the ...normal cells have not been found in light exposed conjunctiva the lower bulbar ...rt or the palpebral conjunctiva.

In 16 patients with keratoconjunctivitis sicca this phenomenon could repeatedly ...e demonstrated in eight patients in 1/5–1/2 of all epithelial cells at every ...vestigation. Furthermore the abnormal cells were characterized by the snake

like type and were found in both eyes The abnormal findings in this group of patients were significantly correlated to the severity of the sicca syndrome (Fig 3).

Patients with abnormal cells were investigated with scrapings from the upper bulbar conjunctiva besides the millipore imprint technique and in no cases could the abnormal cells be found by this method

Twenty four patients were investigated once under the suspicion of Sjögren syndrome 15/24 of these patients had dry eye symptoms and pathological values of Schirmer s test, BUT and rose bengal staining Of these 15 patients with dry eye symptoms six had abnormal cells with typical snake like appearance. In the patients there was no significant difference in the severity of disease in relation to the findings of snake like chromatin in the epithelial cells

Preliminary findings in other patients indicate that the abnormal cells are not restricted to keratoconjunctivitis sicca patients Thus for instance abnormal cells were found in a number of patients with various forms of allergic conjunctivitis

With one exception no abnormal cells were found in the group of normal controls The one exception was a pregnant female with predominance of the straight line type in a few cells

No correlation was found to the use of various artificial tears or to treatment with parenteral steroid

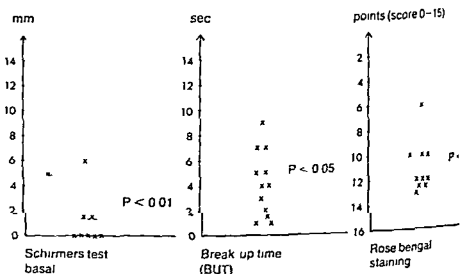


Fig 3

The results of Schirmer s test (basal) break up time and rose bengal staining in keratoconjunctivitis sicca patients (32 eyes) The symbols × or ■ represent mean values of 4–7 monthly investigations and indicate findings of respectively snake-like chromatin or normal chromatin pattern in epithelial cells Mean values of the two groups of eyes are indicated by a dotted line and the *P* values between these values shown.

D scussion

The observed pattern of nuclear chromatin seems undescribed n cellular pathology It is po s bly a spec al nuclear change dur ng cell death caused by some tox c factor The chro nat n arrangement s not an express on of me aphase s nce the nuclear membranes are ntact and no prometaphases or anaphases ere observed

The toxic factor could be derived from the mill pore f lter s nce the abnormal cells were ne er observed n scrap ngs Howe er m llipore f l ers are u ed for the culturing of other cell types w thout seeing the described chang Furthermore one had to expect that a poss ble toxic factor from the m ll pore f e would equall affect a l ep thel al cells and f so the described correla on l e se er ty of ke atoconjuncti t s s cca and the l m tation to the upper bulbar n ct a would be inexplicable

The f nd ngs of abnormal cells were s gn f cantly correlated e se erity of disease Howe er no correlation was found to the presence of l eu a o d factors particularly ANA The observed changes m ght be a result of a d e en es stance to the drying procedure of the diseased and healthy cells The e e he presen e and number of snake l ke nuclei m ght be used as a prognost c Ho e er the significance of the described findings are under further n es gat o

References

Egbert P R. Lauber S & Maurice D M (1977) A s mple conjun tival b ops *Amer J Oph ha* *84* 98 801

nes L T (1966) The lacrimal sec e ory sys em and ts reatmen *Ame J Ophthal 62* 1 60

n M S (19 4) Ex ernal Eye Methods of Exam na on p 76 Scr pto Copenhagen

Norn M S (197) O l and poly nyl alcohol t ea men of kera oconjun ti s s cca *A ta ophthal. (Kbh) 55* 945 950

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TRANSACTIONS OF THE SWEDISH OPHTHALMOLOGICAL SOCIETY 1979

EDITED BY

ULF STENEVI

Meeting in Skovde September 14–15 1979

S Stenkula & G Tornquist *Vitrectomy in retinal detachment*

T Jerndal & M Lundstrom *300 trabeculectomies a follow-up study through three to six years* [illegible]
Trabeculectomy holds its place as an efficient and safe operation in open angle glaucoma but in this study postoperative medical therapy was needed to an increasing extent with time

References

Jerndal T & Lundstrom M (1977) 330 trabeculectomies a follow up study through [illegible] years *Acta ophthal (Kbh)* 55 52
Jerndal T & Lundstrom M (1980) *Acta ophthal (Kbh)* 58 in press

B Lundh & G Lennerstrand *Grating tests in the screening for early glaucoma*
We have determined contrast sensitivity to sinusoidal gratings in patients with glaucoma [illegible] order to see if we could confirm the findings of Arden & Jakobsson (1978) that patients [illegible] early glaucoma and ocular hypertension often showed a subnormal contrast sensitivity [illegible] that the degree of abnormality varied with the grading of the disease

Methods We tested one group of patients with manifest glaucoma and one group of [illegible] in the same age range All glaucoma eyes had normal visual acuity Snellen acuity 0.9 [illegible] We determined contrast threshold for sinusoidal gratings of different spatial frequ[illegible] with the Arden plates and with the pattern displayed on the screen of a cathode ray [illegible] (CRT) We have previously used the CRT method qui[illegible] [illegible]ly in a clinical [illegible] found it to be of high reproducibility

Results With the Arden grating test we found that two out of eleven eyes selected randomly from our eleven normals scored above the normal limit given by Arden Three normals showed a difference between the two eyes that exceeded what Arden considere l as normal In patients with bilateral glaucoma the most affected eye was selected for this study Five out of fifteen glaucomatous eyes were found to have normal contrast sensitiv ty to Arden gratings Eleven of the eyes had visual field defects and four of these score l as n rmals With the CRT method we found normal contrast sensitivity in eight out of ten eyes with pathological Arden score This group included eyes with visual field defects One eye with visual fiels defects had a subnormal CRT contrast sensitivity but a normal Arden score

onclusion Since we were unable to safely differentiate normal from glau omatous eyes with either of the contrast sensitivity methods we conclude that determination of grating thresholds cannot be used as a reliable screening test for early glaucoma

Reference

Arden G & Jakobsson J J (1978) *Inve t Ophthal Visual Sci 17* 23 32

B Naeser *Benign mixed tumour of the lacrimal gland in a 10 year old boy a clinico patholo gical case report*

A slowly growing tumour underneath the lateral part of the right upper eye lid was observed for about three months in a 10 year-old boy The tumour was not dherent to the surrounding tissues Fine needle biopsy displayed monomorpheous cells which in many places were surrounded by eosinophilic fibrillar mucus There was no cellular atypia The histological diagnosis was benign mixed tumour of the lacrimal gland

Computorized tomography showed a highly attenuating process in the anterior and lateral part of the right orbit between the eye globe and the lateral orbital wall There was no retrobulbar extension of the tumour

At operation the tumour was removed through the upper eye lid It had a capsule and was fixed to the lateral part of the lacrimal gland The tumour had a firm consistency and measured 15 × 14 × 14 mm The cut surface was gravish white The histo p thological slides showed the typical picture of a benign mixed tumour with epithelial cells in cords ducts and acini like formations In the loose stroma there were myxomatous and ch ndromatous areas Spinocellular metaplastic changes were occasionally seen There were however no cellular atypia and the whole tumour was surrounded by an intact connective tissue capsule

The present case shows that benign mixed tumours may be found at the age of ten The case also illustrates the great help of fine needle biopsy for the diagn sis f orbital tumours

Symposium

Beta Blockers in the Treatment of Glaucoma

Panel members *B Calissendorff M Pandolf C Törnqu st K Wettr ll A Öhrstr m*

P E Wälinder F B Håkansson & M Lindberg *T molol ophthalmic solut on n the treatment of exfoliatr nd simple glaucoma*

The hypotensive effect of Timolol ophthalmic solution was studied in previously untreat open angle glaucoma (preliminary results were presented at the Swedish ophthalm... meeting 78 09 29)

The study included 68 eyes in 50 patients mean age 68 years There were 50 exf... glaucoma and 18 simple glaucoma with an average intraocular pressure (IOP) bef... treatment of 30 and 28 mmHg respectively Most eyes had visual field defects ... glaucomatous changes of the optic disc

Timolol caused a marked lowering of IOP initially in exfoliative glaucoma, especially in ... eyes with high IOP before treatment The hypotensive effect then decreased and only 16 ... 48 eyes (33%) were controlled (< 22 mmHg) by Timolol alone during nine months, 17 ... (40%) required additional therapy and 12 eyes were operated on One eye was con... with pilocarpine alone

Fourteen simple glaucoma eyes were followed for nine months In eleven eyes (9) I... was controlled with Timolol alone one eye required additional pilocarpine and two eyes w... operated on

In 15 eyes the treatment with Timolol was stopped IOP measurements one to f... later showed an average increase of IOP of 5 mmHg

Three eyes showed a slight punctate keratitis during the treatment with Timolol the d... was discontinued in one eye One 65 year-old patient developed a cystic macular oedema... one eye during treatment with Timolol the drug was discontinued

Conclusions In our material Timolol alone controlled IOP in most simple glaucoma, ... exfoliative glaucoma often required additional therapy

Meeting in Stockholm December 5–7 1979

Symposium

Clinical applications of recent advances in visual physiology

Moderator *G Lennerstrand*

R Granit *Information processing in the visual cortex basic a pects*

G Lennerstrand *VEP and visual function*

Clinical testing of visual evoked potentials or VEP is usually done with pattern re... stimulation of grating or checker board shape An increase in latency of transient VE... diagnostic sign for optic neuritis (Halliday et al 19 3) Steady state VEPs have been use... refraction (Millodot & Riggs 1970) detection of visual field defects (Cappin & Nissim ... for electrophysiological tests on meridional amblyopia (Fiorentini & Maffei 19 ... a... strabismic amblyopia (Sokol 1977)

VEP can also be used for testing binocular vision A method based on binocular inte... has been developed in which prominent VEP depression to dioptic stimulation ... normal binocular functions and an unchanged binocular VEP in comparison wi... monocular response was the mark or disrupted binocular vision due to squint or bin... rivalry (Lennerstrand 1978)

References

Cappin J & Nissim S (1975) Visual evoked responses in the detection of field defects in glaucoma. *Arch. Ophthal. (Chicago) 93* 9–18

Fiorentini A & Maffei L (1974) Evoked potentials in astigmatic subjects *Vision Res 13* 1 81–1/83

Halliday A M McDonald W F & Mushin J (1973) Delayed pattern-evoked responses in optic neuritis in relation to visual acuity *Trans ophthal Soc U K 93* 315–324

Lennerstrand G (19 8) Binocular interaction studied with visual evoked responses (VER) in humans with normal or impaired binocular vision *Acta ophthal (Kbh) 56* 6?8–63"

Millodot M & Riggs L A (19"0) Refraction determined electrophysiologically *Arch Ophthal (Chicago) 84* 272–278

Sokol S (1977) Visual evoked potentials to checkerboard pattern stimuli in strabismic amblyopia In Desmedt J E (Ed) Visual Evoked Potentials in Man New Developments pp 410–417 Clarendon Press Oxford

P Jakobsson *A comparison of different VEP methods for assessment of binocular functions*

Two VEP methods have been compared, regarding their ability to assess binocular functions One method is assumed to reflect binocular competition in the striate cortex (as described above by Lennerstrand) and the other neural summation in the visual areas of the signals from the two eyes

Methods The stimulator is a transparent screen made of squares of polarizing material subtending 30 min of arc at the viewing distance In the first method suggested to reflect binocular competition the pattern was viewed through two polarizing discs one for each eye The discs rotated at different speeds inducing pattern reversal at slightly different rates for each eye The responses were fed through two averagers each phase locked to one stimulus rate. In this manner it was possible to record responses from each eye even during binocular stimulation With the second method based on binocular summation the pattern was viewed through one and the same polarizing disc for both eyes The binocular response in this method represents the combined VEP of the two eyes

Results Eighteen subjects were tested with both methods Ten had normal binocular vision and eight defective binocularity The binocular monocular ratio was calculated This ratio was compared with the subjects stereoscopic acuity measured psychophysically The first method showed fairly good correlation with stereoscopic acuity (correl coeff + 0 "4) while the second method showed poor correlation (corr coeff + 0 34) A negative correlation was expected in the second method

Conclusion A VEP method suggested to evaluate the state of binocular competition in the striate cortex seemed to be the best for assessing the degree of binocular vision and for separating the individuals with normal binocularity from the ones with defective binocular vision A VEP method thought to reflect neural summation in the striate cortex seemed less useful in this respect

J Sjöstrand *Contrast sensitivity determinations in visual disorders*

Determination of the contrast sensitivity function supplements the traditional acuity measurements in quantifying the visual loss for objects larger than the resolution limit. In general two types of CSF impairments have been demonstrated one comprising only the

Res lts The mean fluorescein concentration n the m ddle of he eous body one h after fluoresce n nject on n the 11 non d abet c controls was 4 4 + 3 7 ng ml A fluorescein concentration greater than the mean + 2 SD of controls was regarded as abnormal An abnormal leakage as found n 15 out of the 26 d abetics The mean fluo escein concentra t on one h follow ng injection in the 26 diabet cs was 18 3 ± 18 0 ng ml Diabetics who were beyond partial rem ss on had a more pronounced leakage (21 5 + 18 8 ng ml while the d abet cs still in partial remiss on showed no such abnormal leakage (5 5 + 5 0 ng ml) There was no sign ficant correlation between a defect blood ret nal barrier and age at onset or durat on of the d sease Two patients had an abnormal leakage af er a du ation of the disease less than 2 years wh le other patients with a durat on of more than 15 years did not have an abnormal barrier There was no relat on between a defect blood ret nal barrier and the a al blood glucose value during the examinat on The d abet cs w h an abnormal blood-retinal barr er had a lo er glucosuria ndex during the last year nd ca ng an nadequa e meta lic control in comparison w th those pat ents who had a normal barrier

In conclusion vitreous fluorophotometry seems to be a ery sens ble method for e detect on of blood retinal barr er changes A strict metabol c control may prevent or postpone the appearance of these early retinal changes

Symposium Bleeding in Ocular Surgery

Moderator *M Pandolfi*

Panel members *P Algvere T B a nsen S Stenk la S O terl n*

M Pandolfi *Bleed ng n ocular surgery*

Haemostatic disorders may cause profuse bleed ng at ocular surgery Patients with congenital defects of haemostasis are generally known n Sweden and can be opera ed upon under protect on of subst tut on treatment Acqu red d sorders of haemostas s a e more common and often und agnosed Of special interest are the defects follow ng treatment with aspirin and other non stero d anti inflammatory agents These substances worsen haemostasis by inh b ting the product on of tromboxan wh ch s a potent platelet agg egator These drugs should be w thdrawn one week before operat on

19 9 Year Book of Ophthalmology edited by William F Hughes Pp 366 with illustr Year Book Medical Publishers inc Chicago-London Price dollars 39 75

The Year Book of Ophthalmology 1979 resembles the previous volumes in appearance and quality having the same size and solid binding and being again printed on glazed paper The abundant collection of articles is organized in 14 chapters comprising Lids Lacrimal Apparatus and Orbit Motility Vision Refraction and Contact Lenses Conjunctiva Cornea and Sclera Glaucoma Lens Uvea Vitreous Retina Neuro-ophthalmology Medical Ophthalmology and Drug Therapy Surgery and Basic Sciences and Miscellaneous A final 15th chapter contains 49 questions concerning the subjects treated of in the previous 14 chapters By trying to answer these questions the reader has a chance of controlling whether he she has obtained full benefit of reading the book If not the questions may serve for and lead to a recapitulation of some of the read chapters The contents seem to have been chosen with great care and with a suitable classification within the various groups of subjects

Reading of the book therefore contributes towards prompt and easy information on the latest conquests within the various fields of ophthalmology including practical therapeutic and surgical problems as well as theoretical problems

The great majority of the chapters are kept in a concise form However many of them have references of aid to those who want to go into further details regarding a special subject At the back of the book we find a good subject index and an equally good index to authors

I can accordingly recommend the Year Book of Ophthalmology 1979 to all ophthalmologists and others interested in ophthalmology who in the daily routine feel that they have no possibility of keeping sufficiently up to date with the current ophthalmological literature in journals and recently published books The book under review gives the reader an easy chance of being informed about the latest achievements within ophthalmology To those who are particularly interested and engaged in a special ophthalmological problem the book will hardly bring any new details on this subject but the reader may then enjoy going through the other chapters

K E Rasmussen

ridhecker W Die Glaukome in der Praxis 3rd ed Springer Verlag Berlin Heidelberg New York 1979 DM 19 80

The author s intentions with this book to guide the ophthalmologist in private practice and to inform about practical problems concerning diagnosis and therapy of glaucomas in their different forms has been fulfilled by this pocket book with 6 tables and 64 figures Dr Leydhecker s second intention that the book should provide some sort of information guide for many patients seems not to be convenient in a Danish population not familiar with medical terms

Any field of glaucoma except the scientific is commented on The author s style is clear and concise *and is mostly based on many years of practice*

This is a useful book for the training as well as for the practicing ophthalmologist

At a time when no really satisfactory procedure or treatment exists for glaucoma it seems necessary to have a firmly guiding companion which is found in this book Through including some of the less modern techniques such as tomography the book is sufficiently up-to-date to mention some of the new pharmacological preparations such as timolol and to the few modern forms of drainage operations

Torben B Sorensen

Stadj N Rollungsschielen physiologie – instrumentarium – therapie Kol et Verlag Giessen Kiesweg 23 D-6300 Giessen ISBN 3-922306-00-4 113 pages 35 pictures Price DM 26 –

The title of this book cyclodeviations – physiology instruments and therapy – sounds promising Certainly there is a need for a monograph covering this aspect of strabismology

After commenting on the classical views on the mechanism behind ocular movements the author describes the mode of investigating cyclodeviations in the well-known clinic at Giessen He emphasizes that an investigation using only synoptophore or synoptometer does not give a complete picture of a cyclodeviation The author believes that the preoperative ... should be based on the results of several methods He has designed three new ... and he also stresses the importance of an analysis of after images in combination with synoptometer measurements Some pathological cases are reviewed and the most ... surgical techniques are discussed.

Those strabismologists who are familar with the vocabulary of the Giessener Schule ... find this monograph enjoyable Those who do not will have difficulties in penetrating the ... with its many confusing passages where physiology pathology and short case histories are mixed up There are many shortcomings and the few statistics are never based on ... deviations Those ophthalmologists who had expected a profound discussion of the ... role of cyclodeviations – as the text title suggests – will be disappointed The author's recommendation of a multianalysis of cyclodeviations in all types of ... oculomotor pares horizontal phorias A V syndroms and many other cases, can be theoretical value but is definitely not of practical importance

The short and careless English summary is not a translation of the German one It is a general introduction to the problems and it gives only a vague conception of how cyclodeviations are handled in Giessen

Helveston Eugene M & Forrest D Ellis Pediatric Ophthalmology Practice C V Mosby St Louis Toronto London 1980 303 pages incl subject index and references and a comprehensive series of figures (about every second page) Price 43.50 dollars

The book comprises 14 chapters each representing a cornerstone of examination ... diagnosis and therapy within the various of pediatric ophthalmology There are chapters dealing with sight tests strabismus amblyopia cataract disorders of the lacrimal ... system glaucoma, ptosis diseases of the orbit and retinal diseases in the latter group main stress laid on retrolental fibroplasia retinoblastoma and ... The book also contains sections on infections developmental defects genetics, anaesthesia dyslexia

Of course the book being of a limited size does not engage in detailed discussions of numerous different complexes of problems It crystallizes the authors great clinical practical experience in pediatric ophthalmology being comparable to an ... comprehensible and extremely well illustrated guide book.

The book will doubtless be used even so much as to become ... ver the world because with its concise text and comprehensive exceedingly ... res it represents modern highlights of pediatric ophthalmology

Ste to Memo ial Ho p tal (Hea ls C Binder T D ckert and J Nerup) Centofte
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THE VALUE OF THE OSCILLATORY POTENTIAL IN SELECTING JUVENILE DIABETICS AT RISK OF DEVELOPING PROLIFERATIVE RETINOPATHY

BY

SVEND ERIK SIMONSEN

A prospective long term study of the predictive value of the oscillatory potential in the development of proliferative diabetic retinopathy has been made in 137 diabetics Follow ups 6–8 and 13–15 years later demonstrated that recording the oscillatory potential in juvenile diabetics with a disease duration of more than 5 years is valuable in selecting those at risk of developing proliferative retinopathy within 6 years at any rate The predictive value of the oscillatory potential is probably more limited in women who later become pregnant

Key words diabetic retinopathy – electroretinography – oscillatory potential

vestigations made by Francois & De Rouck (1954) Karpe et al (1958) and Straub 961) have shown that the classical ERG does not exhibit significant changes in abetic retinopathy until very advanced retinopathy is present

In 1962 Yonemura et al by means of another electroretinographic technique owed that the so called oscillatory potential a fast oscillating component of the RG was selectively reduced even in very early stages of diabetic retinopathy hese findings have since been confirmed among others by Sugita et al (1963) monsen (1965 and 1968) Kojima et al (1966) Jacobson et al (1967) Nakajima et l (1968) Brunette & Desrochers (1970) Tassy et al (1971) Armington (1974) and otterberg (1974)

In order to evaluate whether the oscillatory potential is of prognostic value in abetic retinopathy a prospective study was started in 1964

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Materials and Methods

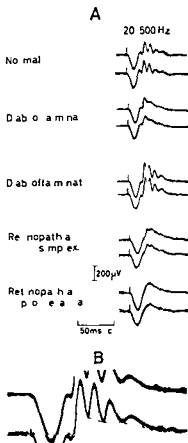
The initial examination was carried out during the period 1964 to 1 ... at the Steno Memorial Hospital Gentofte Denmark while the final reexamination was carried out at the Eye Department, Gentofte Hospital

141 patients representing 275 eyes were included in the study ... four patients (8 eyes) were later excluded from the material due to refraction errors or age exceeding the limits stated in the protocol The corrected material therefore comprises 267 eyes from 137 patients 57 women and 80 men, with insulin dependent diabetes mellitus aged 17 to 50 years who were controlled at regular intervals at the Steno Memorial Hospital a hospital for diabetics In all cases the diabetes had been diagnosed prior to the age of 40 Only 9 of the eyes had a corrected visual acuity ≤ 6 12 the poorest value 6 36 being found in an eye with proliferative retinopathy All were treated with insulin and diet. Only few of the patients showed metabolic dysregulation at the time of examination Patients with refractive errors exceeding three dioptres eye diseases other than diabetic retinopathy consumption of drugs known to influence the electroretinogram, and pregnant patients were primarily excluded The ophthalmological examination included refraction and corrected visual acuity slit lamp examination, ophthalmoscopy colour photographs comprising the central 60 of the fundus and electroretinography

Prior to the study the normal range of the oscillatory potential was evaluated by examining 50 eyes from 26 healthy non-diabetics aged 17–50 years with normal visual acuity refractive errors less than three dioptres normal ophthalmoscopy and normal color vision measured by Ishihara plates

Electroretinography was carried out after 20 min of dark adaptation preceded by ... at least half an hour in the examination room at an illumination of about 5 lux Prior to recording each patient had the procedure thoroughly explained since perfect ... essential for proper performance of the test Maximal dilatation of the pupils was obtained using cyclopentholate 1 0% and neo-synephrine 10% The light stimuli were produced by a ... Xenon stroboscope using a flash energy of 0 1 0 2 and 0 6 J Routine ... of the oscillatory potential was done using a flash energy of 0 6 J The ... was about 100 microseconds the peak luminance at 0 6 J ... being about 3 × 10⁶ lux measured at the cornea Flash in ... order to elicit maximal amplitudes of the oscillatory potent... meister 19 2) The circular mat glass patch of the reflector ... equipped with a small red central fixation light Th... subtending a visual angle of 3° degrees The electr... from both eyes using the Karpe contact lens elect... reference electrode was placed on the middle of th... at the ear lobe The potential was led to an ... recorded by photographing 3–5 superimposed cathode ray oscilloscope DISA[*] The frequen...

500 Hz correspo d ng o lower t me constants of about 100 and 10 m ll econds pectı ely Routıneously record ng of he osc lla ory po en al was done us ng a frequency nge of 90 500 Hz (see F g 1) Measurement of the ampl udes of the s ng e wa elets of he lla ory po entıal was done accord ng to the me hod of S monsen 196 hus obta n ng a mmed alue of the ampl udes The ampl udes of he d ffe en omponents we e a ua ed by cal per square measurements The error of measu emen s was e uma ed to + 5 this error be ng small n comparison w h he recorded ampl ude and the anda d o of the mean



F g 1

shows d fferent ERG s as e ponse o he stronge fla h Ea h ERG n the f gu e cons ts of e superimpo ed responses In ea h of he ERG-pairs the upper reco d ng rep esen s he gh eye wh le he lower ep esents the left e e The ampl udes as shown n B a e he ertical d s an es be ween he p aks of the osc lla ons and the do ed l nes connectıng he r o ghs Thus he a ue f the added amp udes nd ca es the de ation from the maginary smoo h curve

Table VI

The findings at the first follow up shown in Table III are split up in relation to [illegible] of diabetes at the initial investigation. The numbers in brackets denote [illegible] examined eyes presenting proliferative retinopathy at the initial investiga[illegible]

Duration of diabetes at the initial examination (in years)	Oscillatory potential	Ophthalmoscopic appearance (No. of eyes)		
		Unchanged retinopathy	Deteriorated	
			simple retinopathy	proliferative retinopathy
0–5	Hypernormal	7	2	0
	Normal	14	3	0
	Subnormal	5	1	0
6–10	Hypernormal	8	3	0
	Normal	11	9	0
	Subnormal	4	3	1
11–15	Hypernormal	13	0	0
	Normal	13	6	0
	Subnormal	3	2	1 (
16–20	Hypernormal	6	2	0
	Normal	5	6	5
	Subnormal	1	5	1 (
> 20	Hypernormal	6	0	0
	Normal	9	4	0
	Subnormal	0	2	6 (1
Total No.		105	48	9 (1

Table VI shows that the transition to proliferative retinopathy has also tak[illegible] place in those initially presenting hypernormal and normal oscillatory potentia[illegible] regardless of the disease duration.

Deterioration in visual acuity could be demonstrated predominantly amo[illegible] e[illegible] initially presenting subnormal oscillatory potential. At the first follow up (Ta[illegible] VII) none of the eyes initially presenting hypernormal values of the oscil[illegible] potential showed changes in visual acuity. In eyes initially showing values of th[illegible] oscillatory potential within the normal range only 8 out of 85 eyes (9%) ha[illegible]

veloped slight to moderate deterioration in visual acuity However in the group of eyes initially presenting subnormal values of the oscillatory potential no less than ? out of 76 eyes (42%) had developed deterioration in visual acuity and 10 of these were legally blind ($P < 0.001$)

At the second follow up (Table VIII) only 2 out of [illegible] eyes [illegible] initially presenting hypernormal values of the oscillatory potential had developed slight deterioration in visual acuity Among eyes initially showing values of the oscillatory potential within the normal range 34 out of 106 eyes (32[illegible]) had diminished visual acuity 13 of these being legally blind In the group of eyes initially presenting subnormal values of the oscillatory potential no less than [illegible] of [illegible] 59 eyes (69%) had developed deterioration of the visual acuity 29 of these being legally blind ($P < 0.001$) Only three patients initially presenting subnormal values of the oscillatory potential had developed slight cataract with visual acuities ranging from 1?9 to 6 24

Table V

Relationship between the initial value of the oscillatory potential and the ophthalmoscopic fundus changes in 238 eyes of 124 patients at the second follow up The numbers in brackets denote 38 eyes from 19 patients deceased during the follow up period

Initial value of oscillatory potential	No	Diagnostic group	No
Hypernormal	37 (+6)	unchanged (± simple r)	20 (+ 6)
		deteriorated (simple r)	14 (+ 0)
		deteriorated (prolif r)	3 (+ 0)
Within normal range	96 (+ 10)	unchanged (± simple r)	38 (+ 2)
		deteriorated (simple r)	37 (+ 2)
		deteriorated (prolif r)	21 (+ 6)
Subnormal or extinguished			
± simple retinopathy	49 (+9)	unchanged (± simple r)	3 (+ 0)
		deteriorated (simple r)	18 (+ 1)
		deteriorated (prolif r)	28 (+ 8)
with proliferative retinopathy	18 (+ 13)	proliferative retinopathy	18 (+ 13)

Table VI

The findings at the second follow up shown in Table V are split up in relation to the d[illegible] of diabetes at the initial investigation. The numbers in brackets denote eyes pre[illegible] proliferative retinopathy at the initial investigation.

Duration of diabetes at the initial examination (in years)	Oscillatory potential	Ophthalmoscopic appearance (No. of eyes)		
		Unchanged retinopathy	Deteriorated	
			simple retinopathy	proliferative retinopathy
0–5	Hypernormal	3	4	[illegible]
	Normal	9	[illegible]	3
	Subnormal	1	4	1
6–10	Hypernormal	4	[illegible]	0
	Normal	[illegible]	6	9
	Subnormal	0	4	6
11–15	Hypernormal	8	3	0
	Normal	9	10	3
	Subnormal	1	5	10 ([illegible]
16–20	Hypernormal	[illegible]	2	1
	Normal	4	9	11
	Subnormal	0	4	16 ([illegible]
> 20	Hypernormal	6	0	0
	Normal	[illegible]	5	1
	Subnormal	1	[illegible]	3 ([illegible]
Total No		[illegible]	[illegible]	[illegible] (+3[illegible]

Discussion

This represents the first prospective study made to estimate the prognostic value o[illegible] the oscillatory potential in diabetic retinopathy.

After the initial recording of the oscillatory potential the patients were re[illegible] examined ophthalmoscopically and visual acuity recorded 6–8 years and 13–1[illegible] years later. 78% of the patients were reexamined 6–8 years after the in[illegible] investigation and 91% were reexamined 13 to 15 years after the initial invest[illegible] including the last known status of the decreased in the follow up period.

Table VII

Visual performance of 208 eyes of 107 patients at the first follow up. The numbers in brackets denote the patients with subnormal oscillatory potential initially presenting with proliferative diabetic retinopathy

Initial oscillatory potential	Initial visual acuity (1961–66)		Visual acuity 1972					
	Snellen value	n	*Unchanged*	*Deteriorated*				
				6/9	6/12–6/18	< 6/18 < 6/36	≦ 6/60
Hypernormal (n = 47)	6/6	47	47				
Normal (n = 85)	6/6	81	73	5	2	1	
	6/9	3	3				
	6/12	0	0				
	6/18	1	1				
Subnormal (n = 57 (+19))	6/6	55 (+10)	36 (+6)	12 (+9)	3	1	3 (+)
	6/9	1 (+7)	1 (+1)		0 (+9)		0 (+1)
	6/12	1 (+1)			1		0 (+1)
	6/18	0 (+1)			0 (+1)		

Table VIII

Visual performance of 238 eyes of 124 patients at the second follow up. The numbers in brackets denote those patients with *subnormal oscillatory potential initially presenting with proliferative diabetic retinopathy*

Initial oscillatory potential	Initial visual acuity (1961–66)		Visual acuity 1979					
	Snellen value	n	Unchanged	Deteriorated				
				6/9	6/12–6/18	< 6/24–< 6/36	≦ 6/60
Hypernormal (n = 13)	6/6	13	11	2			
[illegible]	[illegible]	10	72	[illegible]	[illegible]		[illegible]
	[illegible]	[illegible]			1		
	6/6	[illegible] (+1)	[illegible]0 (+4)	9 (+3)	11	– (+)	11 (+3)
	6/9	[illegible] (+10)	0 (+)		–	0 (+1)	– (+7)
	6/12	1 (+5)			1 (+1)		0 (+1)
	6/18	0 (+9)					0 (+9)
	<6/18	0 (+4)	0 (+4)				0 (+)

Neither the blood sugar level at the time of the investigation nor intravenous infusion of glucose was found to influence the size of the oscillations thus showing that short term dysregulation does not influence the oscillatory potential

Alterations in the oscillatory potential in diabetics without retinopathy must reflect functional changes in the neurophysiologic properties of the retina before ophthalmoscopical changes are detectable

The reexamination 6–8 years after the initial investigation confirmed the assumption that measurement of the oscillatory potential is of predictive value in juvenile diabetics since by this time 54% of those belonging to the subnormal group had developed proliferative retinopathy while only 6% of those in the normal range had developed proliferative retinopathy If those who developed proliferative retinopathy during pregnancy are excluded only 2% of those in the normal range had developed proliferative retinopathy None in the hypernormal group developed proliferative retinopathy

The predictive value of the oscillatory potential is however restricted to those diabetics with a duration of the disease of more than five years since proliferative retinopathy could not be demonstrated 6–8 years later in those who had had diabetes for less than five years at the initial investigation

The normal or hypernormal oscillatory potential therefore to a very great extent excludes the development of proliferative retinopathy within the next 6–8 years

The reexamination 13–15 years after the initial investigation showed however that 7% in the hypernormal group 26% in the normal range and 62% in the subnormal group had developed proliferative retinopathy

The predictive value of the oscillatory potential is therefore mainly restricted to a period of 6–8 years in juvenile diabetics with a duration of diabetes of more than 5 years at the time of recording the oscillatory potential

As shown in this material determination of visual acuity is of no predictive value in diabetic retinopathy Retrospectively those developing reduced vision were mainly those presenting proliferative retinopathy at the initial investigation or those who had developed proliferative retinopathy in the observation period and predominantly those initially presenting reduced oscillatory potential

Conclusion

Measurement of the oscillatory potential in juvenile diabetics with a disease duration of more than five years is of great predictive value in selecting those at risk of developing proliferative retinopathy

The predictive value of the oscillatory potential can be extended to at least 6–8 years

The predictive value of the oscillatory potential is doubtful in women who later become pregnant

Acknowledgments

The author wish to express his gratitude to Drs Kim Frost Larsen and Hans-Walter Larsen for fruitful discussion and friendly support during the preparation of this manuscript.

References

Algvere P (1968) Clinical studies on the oscillatory potentials of the human electroretinogram with special reference to the scotopic b-wave *Acta ophthal (Kbh)* 46 993–1024

Armington J C (1974) The electroretinogram Acad Press New York

Brunette J R & Desrochers R (1970) Oscillatory potentials A clinical study in diabetics *Can J Ophthal* 5 373 380

Francois J & De Rouck A (1954) ERG dans la retinopathie diabetique et dans la retinopathie hypertensive *Acta ophthal (Kbh)* 32 391–404

Gjotterberg M (1974) The electroretinogram in diabetic retinopathy *Acta ophthal (Kbh)* 52 521–533

Jacobson J H Hirose T & Popkin A B (1967) Oscillatory potential of the electroretinogram relationships to the photopic b-wave in humans *AMA Arch Ophthal* 8 58 68

Karpe G Kornerup T & Wulfing B (1958) The clinical ERG *Acta ophthal (Kbh)* 36 281–291

Kojima K et al (1966) ERG in diabetes In Nakajima A (Ed) (1966) Retinal degeneration ERG and optic pathways Fourth ISCERG Symp Hakone 1965 pp 1 0 1 5 *Jap J Ophthal 10 Suppl*

Nakajima A & Sugimachi Y (1968) The clinical value of ERG in metabolic disorders In Francois J (Ed) The Clinical Value of Electroretinography Fifth ISCERG Symp Ghent 1966 pp 243 249 Karger Basel

Simonsen S E (1965) Electroretinographic study of diabetics Preliminary report *Acta ophthal (Kbh)* 43 841 843

Simonsen S E (1968) ERG in diabetics In Francois J (Ed) The Clinical Value of Electroretinography Fifth ISCERG Symp Ghent 1966 pp 403–412 Karger Basel

Straub W (1961) Elektroretinographische Untersuchungen bei Retinopathia diabetica *Klin Mbl Augenheilk* 63 81 83

Sugita Y Tanabe S & Awaya S (1963) The ERGs of human diabetes and experimental diabetes in dogs *Acta Soc Ophthal Jap* 67 1137 1144

Tassy A Jayle G E & Castaut Maysou M (1971) Electroretinographie clinique et potentiels oscillatoires dans le diabete et dans la cataracte du sujet diabetique *Arch Ophtal Paris* 31 413 4

Wachtmeister L (1972) On the oscillatory potentials of the human electroretinogram in light and dark adaptation *Acta ophthal (Kbh) Suppl* 116 1 3

Yonemura D Aoki T & Tsuzuki K (1962) Electroretinogram in diabetic retinopathy *AMA Arch Ophthal* 68 1 4

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OSCILLATORY POTENTIAL AND NYCTOMETRY IN INSULIN DEPENDENT DIABETICS

BY

KIM FROST LARSEN[1] HANS WALTHER LARSEN and
SVEND ERIK SIMONSEN

The study draws a comparison between the oscillatory potential of the electroretinogram and the initial dark adaptation measured by nyctometry with the aim of assessing the predictive value of nyctometry in juvenile diabetics The study included 61 insulin-dependent juvenile diabetics aged 18-49 years with a disease duration of more than five years A statistically highly significant correlation could be demonstrated between alterations in the oscillatory potential and the initial dark adaptation The results justify the assumption that nyctometry can be used as an easily handled clinical tool in selecting those at risk of developing proliferative retinopathy in their subsequent 6-8 years

Key words diabetic retinopathy – electroretinography – oscillatory potential – dark adaptation – nyctometry

The well-documented beneficial effect of photocoagulation on proliferative diabetic retinopathy is mainly restricted to early stages of neovascularization (Diabetic Retinopathy Study Research Group 1976 Hamilton et al 1976 Cheng et al 1978 Oosterhuis et al 1979) making it crucial that the proliferative cases are detected as early as possible Relying on ophthalmoscopy the current screening method

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incipient neovascularization may be missed and even the most thorough ophthalmoscopy does not exclude the development of neovascularization within a period. Proper detection of early proliferative retinopathy based on visible morphological changes therefore requires control examinations at an almost impracticable frequency. Therefore there is a need for a quick and easily handled screening test that will predict with reasonable certainty the course of simple retinopathy in the individual diabetic for a number of years. Such a test would make it possible to identify patients who might delelop proliferative diabetic retinopathy and follow them closely.

In 1962 Yonemura et al. showed that the so-called oscillatory potential, a high oscillating component of the human electroretinogram, was selectively reduced even in early stages of simple diabetic retinopathy. This finding was later confirmed by Simonsen (1965) who also found diminution in the oscillatory potentials in diabetics without ophthalmoscopically visible fundus changes and suggested that the reduction of the amplitudes of the oscillatory potential reflected ophthalmoscopically invisible pathophysiological changes preceding the development of proliferative diabetic retinopathy (Simonsen 1968). In the belief that determination of the oscillatory potential in juvenile diabetics could predict the course of retinopathy in the individual case, a prospective study on the prognostic value of the oscillatory potential was started in 1964. However, even though this assumption was confirmed during the period of investigation (Simonsen 1980), we realized that proper recording of the oscillatory potential, apart from being inconvenient to the patient, is too time- and staff-consuming to be suitable for screening. In an endeavour to develop a simple test carrying the same predictive information as the oscillatory potential, we recalled an article published by Gliem & Schulze (1975). In a group of 153 diabetics they found that with increasing severity of diabetic retinopathy there was a progressive deterioration in both the initial 2 min of dark adaptation and the ability to overcome a subsequent glaring. Their results were obtained by nyctometry, a standardized, quick and simple procedure measuring the macular adaptation. For unknown reasons these authors have not further explored their original observations.

Interestingly, the distribution of the results of initial adaptation in relation to the degree of retinopathy obtained by Gliem & Schulze (1975) showed a close resemblance to the distribution of Simonsen's electroretinographic results (Simonsen 1968). We assumed that such an apparent conformity could hardly be accidental but might rather be due to functional changes in the diabetic retina affecting both the initial course of dark adaptation and the generation of the oscillatory potential.

Therefore a comparative study of nyctometry and oscillatory potential was made in a group of insulin-dependent diabetics.

Material and Methods

The comparative study of the oscillatory potential and nyctometr t 30 omen and 31 men with insulin-dependent diabetes mellitus r the median age being 31 4 years All were selected at random among the Steno Memorial Hospital The duration of diabetes ranged f or l mean duration being 14 6 years In all patients the disease had been d the age of 40 All were treated with insulin and diet and all received insulin daily dose of insulin ranged from 0 35 to 1 54 IU kg the mean total dose b

Primary exclusion criteria were arterial hypertension nephr h ther l neuropathy visual acuity less than 6/9 refractive errors exceeding thr e diseases other than diabetic retinopathy consumption of drugs known to fl nce on the electroretinogram and pregnancy

Prior to the actual admission every patient had for years been controlled t intervals of two four months at the outpatient clinic The main reason for the a u l dm sion was a need for minor adjustment of the metabolic regulation

The ophthalmological examination included refraction and corrected ual acuity slit lamp examination ophthalmoscopy colour photographs of the fundus fluoresce n angiography electroretinography (oscillatory potential) and nyctometry

Prior to the study electroretinography and nyctometry was performed n 15 eyes and 40 eyes respectively from healthy volunteers aged 23–47 years

Nyctometry was performed on both eyes after about 15 min stay in the dimly illuminated examination room The recording was done monocularly with the pupil unmedicated the opposite eye being tightly covered with an eye pad in order to minimize interocular light adaptation The recording was performed by means of the registration nyctometer Registrier Nyktometer) originally developed by Comberg and manufactured by VEB Carl Zeiss (Jena GDR) In the present design the registration nyctometer is equipped with a standard test programme which is automatically completed within only 6 5 min thus making it suitable for group examinations Nyctometry has gained wide application as an easy screening method for night blindness among military personnel and civilian lorry-drivers and for that purpose different authors independently have examined large numbers of healthy persons in order to settle normal values for different age groups mono- and binocularly respectively (Lehnert & Schmidt 1966 Sack 1968 Broschmann 1969 Patz 1969 Hartlepp et al 1970) The patient looks through an optical system nto uniformly white-coloured globe in which a diminutive sight test chart is placed in an opening just opposite the patient s eye (or eyes) The test signs are numbers in random order (5 in each line) and 10 lines of different sizes correspond to visual acuities ranging from 0 1 to 1 0 The order of the lines can be changed by the examiner outside the apparatus The sight test chart is indirectly illuminated giving a constant luminance of 0 5 asb (0 16 cd m² (or nt)) By means of the optical system the test types are pictured in the patient s far point thus making the reading independent of the accomodative state To the right of the sight test chart there is another opening for the glaring light The illuminance of the glaring light is 30 lux and its angle to the sight line 8 degrees The test programme consists of three separate steps 1) In the first 3 min the eye is adapted to a strong uniformly white background illumination the luminance being 7000 asb (about 2200 cd/m²) After this light adaptation period the light switches off and 2 n the following 2 min the initial phase of dark adaptation (the instant adaptation) is recorded In the dark globe only the faintly illuminated sight test chart is now visible The patient is asked to read the test signs in the uppermost line (corresponding to a

visual acuity of 0 1) as soon as possible and when at least 4 of 5 optotypes are correctly to advance successively to the following line The instant adaptation is thus recorded as increase in visual acuity as a function of time 3) The last step is a measure of the sensitivity to glare in which the patient s increase in visual acuity is tested during exposure to constant glaring light During the glare the luminance of the sight test chart is successively from the standard (0 5 asb) to 4 (1 3 cd/m²) and finally to 3? asb (10 cd/m²) intervals of 27 seconds The examiner continuously transcribes the patient s reading on a rotating drum thereby drawing an adaptation curve In this way the initial [illegible] adaptation and the sensitivity to subsequent glaring are recorded graphically as an visual acuity as a function of time The recorded curve is finally compared to superimposed curves according to age showing the normal ranges within the 2 5% and 97 5% percentiles The different light sources of the apparatus were calibrated at regular intervals to ensure constant illumination

Prior to the recording each patient had the procedure thoroughly explained since [illegible] cooperation is essential for proper performance of the test

Prior to electroretinography fundus photography and fluorescein angiography the pupils were dilated with tropicamide (Mydriacyl®) 0 5% and cyclopentolate (Cyclogyl®) 1%

The oscillatory potential was determined shortly after nyctometry and [illegible] as described in Simonsen s study (1968) Recording was done on Polaroid® film and the amplitude of the oscillatory potential was measured as the mean value obtained from 3 consecutive electroretinograms (Fig 1) Due to the technical arrangement only one eye (always the left) could be examined

Retinal fluorescein angiography was performed after the ERG A Kowa RC-Wide [illegible] (42) fundus camera equipped with Kodak W 15 and Kodak W 56 interference filters [illegible] excitation and background barrier was used No adverse effects from fluorescein [illegible] recorded All angiograms were assessed independently by the authors

In each eye the following classification of retinal changes was used based on fundus photography and fluorescein angiography 1) no retinopathy 2) maximally 3 microaneurysms 3) more than 3 microaneurysms with or without retinal haemorrhages and additionally with hard exudates 5) proliferative retinopathy with neovascularization [illegible] peripherally located 6) proliferative retinopathy with prepapillary neovascularization

The ophthalmological examinations were carried out in one day

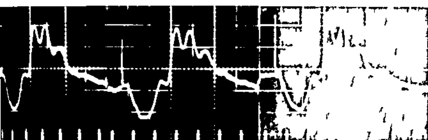
In each case informed consent was obtained prior to the investigation

The Spearman correlation coefficient was calculated in the statistical analysis of the data

Results

The mean value ($\bar{x}$) of the oscillatory potentials obtained from the normal volunteers was 273 µV the SD being 21 µV In his comprehensive study Simonsen (1968) found a normal range ($\bar{x} \pm 2$ SD) of 223–317 µV The results of nyctometry from the normal volunteers all fell within the normal range

The results of nyctometry were classified into three main groups 1) subnormal nyctometry denoting values below the 2 5% percentile of the normal range 2) values within the normal range 3) hypernormal values exceeding the 97 5% percentile



F g 1

\\cilla ory po en als from a 26 year old d abet c woman Tl   a e
easu ed as the mean value of 3 consecutive electroretinograms   q a e
corresponds to 110 μV and the time s denoted by the underl\

Tables I and II show the results of the comparative st l   l s
f n ctometry are divided into the three main groups
scillatory potential corresponding to these are shown l
bd s on of the results of nyctometry is made to de i
eparation in the mean values of the oscillatory potential
roup In the subnormal group performances with n 2 m r
mity have been classified as severely reduced nyctometr
hem from subnormal results slightly below the lo c
qu distant division of the normal range the recorded \
ato low m ddle and high zones of the normal range

Table I

The correlation between nyctometry and oscillatory potent al (added ampl tudes)

	No of eyes	Osc llatory poten al (μV	
		x ± SD	Range
Nyctometry			
Reduced	25	71 ± 15	0 180
Normal	30	263 ± 9	175 385
Hypernormal	6	360 ± 21	935 405

The results of nyctometry are d vided into three ma n groups The mean values ($\bar{x}$ + SD) of the ampl tudes of the osc llatory potent al correspond ng to these groups are markedly separated ($P < 0.01$)

Table II

The correlation between nyctometry and oscillatory potential (O.P.) (added amplitudes)

	No. of eyes	Oscillatory potential (µV)	
		$\bar{x} \pm$ SD	Range
Nyctometry			
Severely reduced	18	28 ± 18	0–110
Subnormal	7	116 ± 9	0–180
Normal range			
Low	7	210 ± 8	[illegible]
Middle	13	256 ± 9	[illegible]
High	10	305 ± 13	[illegible]
Hypernormal	6	360 ± 21	335–403

Even if the results of nyctometry are further subdivided (see text) no overlapping exists between the corresponding mean values of the amplitudes of the oscillatory potential

Table III

The results of nyctometry (n = 122 eyes) in relation to the stages of diabetic retinopathy

Diagnostic group	Nyctometry					
	Severely reduced	Subnormal	Normal range			Hypernormal
			Low	Middle	High	
No retinopathy			4	19	8	4
≤ 3 m.a.				12	4	[illegible]
> 3 m.a.						
± haemorrhages		2	7	8	[illegible]	
with hard exudates	3	11			1	
Proliferative						
Retinopathy						
peripherally	7	[illegible]				
prepapillary	[illegible]					

Severely reduced values of nyctometry are only found in advanced stages of the retinopathy

Analysis of the numeric values of the oscillatory potential and the nyctometry revealed a statistically significant correlation the correlation coefficient r = 0 37 corresponding to a P value less than 0 01

When the values of nyctometry are compared to the degree of diabetic retinopathy in the same eyes (Table III) it is apparent that the eyes showing no or only slight retinopathy display normal nyctometry while severely reduced values of nyctometry are only found in advanced stages of diabetic retinopathy

Discussion

Diminution or extinction of the oscillatory potential has been found to be a feature of advanced diabetic retinopathy Moreover the oscillatory potential tends to diminish with increasing severity of retinopathy and finally to be extinguished in proliferative retinopathy (Simonsen 1965 Brunette & Desrochers 1970 Galloway et al 1972 Gjotterberg 1974)

The demonstration of reduced values of the oscillatory potential not only in eyes presenting advanced diabetic retinopathy but also in eyes without or with only slight retinopathy indicates that electrophysiological disturbances precede ophthalmoscopically visible changes (Simonsen 1968)

Recording of the oscillatory potential in juvenile diabetics with a duration of the disease longer than 5 years is valuable for identification of those at risk of developing proliferative retinopathy A normal oscillatory potential excludes with great certainty the development of proliferative retinopathy for at least 6 years The predictive value of the oscillatory potential is probably more limited in diabetic women who later become pregnant (Simonsen 1980)

However recording of the oscillatory potential is time and staff-consuming and therefore not as suitable for screening as nyctometry

The present demonstration of progressively reduced initial dark adaptation in relation to increasing degrees of diabetic retinopathy is in accordance with the findings of Gliem & Schulze (1975) Reduction of the initial dark adaptation has also been reported in macular diseases (Batra & Paul 1967 Henkind & Siegel 1967 Severin et al 1967)

Dark adaptation is a complex function consisting of photochemical neural receptor and network adaptation the total resultant achievement being an optimized interaction of all three mechanisms (Virsu 1978) Although the mechanisms responsible for the increased recovery time in the initial phase of dark adaptation are not known the phenomenon appears related to disturbances primarily in the neural network adaptation

Examination of the total course of dark adaptation using e.g. the Goldmann-Weeker adaptometer has failed to show abnormalities even in advanced stages of diabetic retinopathy (Cambie 1979). However, this procedure does not permit detailed study of the initial phase of dark adaptation.

The highly significant correlation between alterations in the oscillatory potential and the initial dark adaptation in diabetic retinopathy documented in this study suggests a common mechanism responsible for both the reduction of the oscillatory potential and for the initial phase of dark adaptation.

Microelectrode investigations in animal retinae (Brown 1968) and clinical observations in man (Armington 1974) indicate that the oscillatory potential originates in the middle retinal layers, especially in the inner nuclear layer (Wachtmeister & Dowling 1979). At present it is not exactly known which cell type acts as the generator of the oscillations.

The site of the neuronal mechanisms of the dark adaptation is likewise believed to be located to the inner nuclear layer (Dowling 1967). This might therefore also be influenced by the same functional disturbances which suppress the generation of the oscillatory potential. Therefore, it is tempting to speculate that the reduction of the initial phase of the dark adaptation which can be measured by nyctometry reflects the functional counterpart of those early pathophysiological changes which may precede a transition into changes of proliferative diabetic retinopathy.

In two separate studies (Andersen et al. 1980, Frost Larsen et al. 1981) a significant improvement in the dark adaptation has been demonstrated in newly diagnosed juvenile diabetics after a 10-day period of superregulation in the biostator. Furthermore, in a group of juvenile diabetics selected for home monitoring of the plasma glucose level and subsequent self adjustment of the daily insulin dose, a significant improvement in nyctometry could be demonstrated only in the patients achieving better long term (10-12 months) metabolic regulation. This indicates that in metabolic dysregulation the results of nyctometry are reversible to a certain extent provided the reduced values of nyctometry are mainly due to functional changes in the retina. In cases without dysregulation of the diabetes, reduced values of nyctometry reflect irreversible functional changes in the retinae, in due course probably producing progressive morphological changes, which in most cases lead to proliferative retinopathy.

The significant correlation of the oscillatory potential and nyctometry in juvenile diabetics with a disease duration for more than five years justifies the assumption that nyctometry can be used as an easily handled clinical tool for identification of those at risk of developing proliferative retinopathy within the subsequent [illegible] years.

The probable predictive value of nyctometry indicated by this comparative study is being further investigated in a prospective study now in progress.

Acknowledgments

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References

Andersen A R Andersen J K Lørup B Frost Larsen K Christiansen J S & Deckert T (1980) Self monitoring of blood glucose *Acta End crinol (Kbh) 94 S ppl 23 3*

Armington J C (1974) The electroretinogram Acad Press New York

Batra D V & Paul S D (1967) Macular illumination tests in central serous retinopathy *Amer J Ophthal 63* 146

Broschmann D (1969) Lichtsinnuntersuchungen mit dem Registrier Nyktometer des VEB Carl Zeiss Jena zur Beurteilung der Kraftfahrtauglichkeit *V rk M d 16* 74 81

Brown K T (1968) The electroretinogram its components and their origins *Vision Res 8* 633–677

Brunette J R & Desrochers R (1970) Oscillatory potentials A clinical study in diabetics *Canad J Ophthal 5* 373–380

Carbe E (1979) Functional results following pan retinal photocoagulation In Palo Alto Course on Pathogenesis and Treatment of Diabetic Retinopathy p 1–5 Stanford University School of Medicine

Cheng H Hamilton A M Townsend C & Kohner E M (1978) Photocoagulation in diabetic retinopathy 1 Indications and results *Int Ophthal Cl n 18* 91 106

Diabetic Retinopathy Study Research Group (19 6) Preliminary report on effects of photocoagulation therapy *Amer J Ophthal 81* 383–396

Dowling J E (1967) The site of visual adaptation *Science 155* 973–279

Frost Larsen K Christiansen J C & Parving H H (1981) Improvement of dark adaptation and electroretinogram following short term superregulation of recently diagnosed insulin dependent juvenile diabetics To be published in Diabetologia

Galloway N R Wells M & Barber C (19 2) Changes in the oscillatory potential in relation to different features of diabetic retinopathy In Arden G B (Ed) The Visual System Ninth ISCERG Symp Brighton 1971 pp 295–307 Plenum Publishing New York

Gjøtterberg M (19 4) The electroretinogram in diabetic retinopathy *A ta Ophthal (Kbh) 52* 521–533

Gliem H & Schulze D P (1975) Sofortadaptation Blendungsempfindlichkeit und diabetische Retinopathie *Kl n Mbl A genheilk 166* 766–769

Hamilton A M Townsend A M Khoury D & Gould E (1976) Treatment of new vessels on the disc in diabetic retinopathy *Trans Ophthal Soc U K 96* 228

Henkind P & Siegel I M (1967) The scotometer A device for measuring macular recovery time *Amer J Ophthal 64* 314–315

Jähnert W & Schmidt R (1966) Normalwerte am Registrier Nyktometer von VEB Carl Zeiss Jena *Verk Med 13* 314 321

Ortlepp J, Heydenreich A, Schmautz K. H. & Geyer C. (19[illegible]) M[illegible] und [illegible] Normalwerte der Sofort adaptation und Blendempfindlichkeit in [illegible] kett. *Klin. Mbl. Augenheilk. 158* 652–663

Oosterhuis J. A., Beintema M. R., Lemkes H. H. L. M., Nikkels R. & Terpstra J. [illegible] Photocoagulation treatment in diabetic retinopathy. A two year pre- and [illegible] post treatment study. *Docum. ophthal. 48* 101–169

Patz H. (1969) Untersuchungen über die Sofortadaptation mit dem Registrier-[illegible] des VEB Carl Zeiss Jena. *Verh. Med. 16* 81–88

Sack E. (1968) Altersabhängige Normwerte bei der Nyktometrie. *Verk. Med.* [illegible]

Severin S. L., Tour R. L. & Kershaw R. H. (1967) Macular function and the photo[illegible] *Arch. Ophthal. (Chicago) 77* 2–7

Simonsen S. E. (1965) Electroretinographic study of diabetics. Preliminary report. *Acta ophthal. (Kbh.) 43* 841–843

Simonsen S. E. (1968) ERG in diabetics. In: Francois J. (Ed.) The Clinical Value of Electroretinography. Fifth ISCERG Symp. Ghent 1966, pp. 403–412. Karger, Basel.

Simonsen S. E. (1980) The value of the oscillatory potential in selecting juvenile diabetics at the risk of developing proliferative retinopathy. *Acta ophthal. (Kbh.) 58* [illegible]

Virsu V. (1978) Retinal mechanisms of visual adaptation and afterimages. [illegible] 84–96

Wachtmeister L. & Dowling J. E. (1979) Laminar profile study of the oscillatory potentials of [illegible] vertebrate electroretinogram. In: Tazawa Y. (Ed.) Proceedings of the sixteenth ISCERG Symp. Tokyo 1978. *Jap. J. Ophthal.* 355–360

Yonemura D., Aoki T. & Tsuzuki K. (1962) Electroretinogram in diabetic retinopathy. *Arch. Ophthal. (Chicago) 68* 19–24

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OPHTHALMIC CHANGES FROM AGE OF 10 TO 18 YEARS

A longitudinal study of sequels to low birth weight
I Refraction

BY

HANS C FLEDELIUS

A report is gi en on refractive change (Δ R) from age of 10 to 18 years The 19 9 follow up comprises 13 persons who had earlier (around 19 0) participated in a larger in estigation into ophthalmic sequels to a low birth weight (n = 539)

In general (12 out of 13) there is a shift towards lower dioptric alues (increase in refraction) Seven remained static while three showed a slight decrease in refraction (0 25–0.5 D)

Adult emme and hypermetropia how a median Δ R about 0 D (increase) during adolescence against median values of 1 and 2.5 D in juvenile myopia, of ex prematures and full-terms respectively With a median Δ R of 1 2 D myopia of prematurity occupies an intermediate position (21 eyes of 13 subjects) Except for this subgroup there is no evidence that low birth weight has influenced refractu e distribution

With a (planned) skewing towards myopia, the 19 9-sample cannot be considered epidemiologically representative as was the original 19 0-material Concerning the latter the 18- ear incidence of myopia is given as 1 6% for ex prematures and 13 1% for fullterms *(m nimum figu es* based on school medical records)

Key ord ophthalmic sequels – prematurity – low birth weight – longitudinal stud – adolescence – refraction – juvenile myopia – myopia of prematurity – refractive change

Received May 29 1980

Despite considerable interest in the functic nal and morphc logical deve ...
the young eye there are few major projects in the literature that ...
subject This is especially true as regards longitudinal studies of refrac ...
vision during ch ldhood and adolescence

The present study is meant to reduce th s gap in the l eratu e. ...
of part of the ch ldren from an earlier cross-sectional study ... deals with ...
changes from the age of 10 to the age of 18 years (Fledelius ...
further laid on the possible long term effects of a very low birth weight.

Matenal

The present follow up study comprises 15 18-year-old Danes who had ...
exam nation around the age of 10 as part of a larger scale ...
sequels to a very low b rth weight.

The sample deri es from The Un vers ty H sp tal (Copenhagen ...
S gn ficance of Gestation and Deli ers for the Hea th and De elopment of the ...
designates a longitud nal paediatric study of 6000 pregnancies ...
abortions over 250 g (Zachau Christiansen Thes s 19 ?)

In my 10-year study (Fledel us 19) 30? ... h weight ers LBW < ...
full term controls (FT BW 3-4000 g) attended f r ... phthalmic assessment ...
rates of those nvited a representati e picture was bta ned f he two groups

In 19 9 a grant made it poss ble to re-exam ne part f the 559 children f ...
1969- 9 n estigat on (n the following called the 1970-study) In ... were ...
to those where a follow up was cons dered of special nte est ...
the 19 0-study The 19 9-criteria were

1) Both b rthwe ght groups (< 2000 g and 3-4000 g) were to be fairl represented
2) Among the ex prematures emphas s was la d n the lower birthweights ...
3) All refracti e groups should be included bu wh le emmet opes and ...
randomly sampled from the 19 0-cases ... was a tempted ... examine ...
(myopic at 19 0-status r later developed ... from medical ...
records)
4) Aga n considering the m opes those ... of prematurit ...
encouraged to attend
5) For practical purposes those who had ... mean me settled ...
Copenhagen were not in ed

From this t s e iden that the 1979-follow up d es not trul reflect ...
the two basic b rth weight groups from 19 0 ... 1979 ...
original representati ... has been lost Th s ... be kept n mind ...

Composit on of the 1979 senes

The low birth weight group (LBW) c mprised ... young Da es and there were ...
controls (FT) The number of rep rted ex prema u es was however ...
exclusion of one case This was a female w h a rather ad anced ...

Table I

Birth weight distribution (and mean values) in the basic ex premature group of 1970 and in the fraction with a 1979 follow up

	Number of ex prematures examined around 1970 (n = 309)	Number of ex prematures with ophthalmic follow up 1979 (n = 0)
Birth weight < 1000 g	5	1
BW 1001 – 1250 g	21	8
BW 1251 – 1500 g	64	6
BW 1501 – 1750 g	93	17
BW 1751 – 1999 g	109	11
BW ≥ 2000 g as co-twin or co-triplet to one from the above BW-classes	17	9
Mean age at examin	10 3	18 4
Mean birth weight	1663 ± 283	1561 ± 249

plasia and myopia of prematurity (J No 519 8 Fledelius 19 6) Uveitis and phthisis bulbi explained axial eye measurements remote from physiological range and refraction values could not be stated due to opaque media Her data would weight unduly if entered into the statistics of the morphologically and functionally normal eyes

Selection of the lower *birth weight classes* (in 19 9) is reflected by Table I which comprises birth weight distribution of the ex prematures examined 19 0 and the 19 9-1 BW group

Selection according to *refraction* is shown by Fig 1 It is evident that the myopes from their 19 0-percentages have been concentrated above representativity – due to inclusion into the 19 9 study of only a *small* proportion of the available hyper and emmetropes

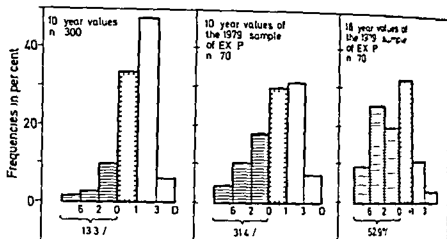
Methods

Cycloplegic refraction was measured by retinoscopy on both occasions Subjective confirmation was obtained with lenses in a trial frame and the customary 6-metre Snellen type The results are given as *spherical equivalent* i e the average between the refractive values of the two main meridians

The refractive change (Δ R) during the period was calculated as the 1970-value minus the 1979-value recorded with one decimal This means that dioptric shifts towards myopia (increase in refraction) are given a positive sign

All reported eyefindings are based on personal examination results The exception is the use of information from school medical records which served the purpose of tracing *new*

EX-PREMATURES



Refractive values (in Dioptr)

FULL-TERMS

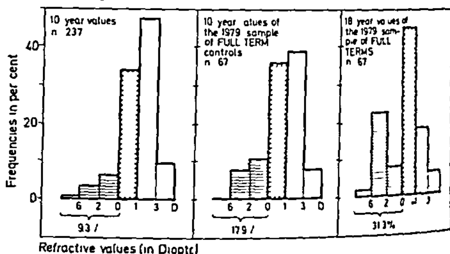


Fig 1

Distribution of refractive classes of low birth weighters (top) and full terms (bottom). The selection of myopic cases for re-examination is apparent from the hatched ... diagrams show the *total* 10-year group (left) and the fraction with an 18-year f... (10-year values in the middle 18-year values right) Emmetropia is shown ...

cases of myopia (because such cases were wanted for follow up) The information ... utilized to give an estimate of the 18 year incidence of myopia in the (f... 1970-sample

As part of the project other ophthalmic examinations were also performed. These are ... dealt with in separate publications which are in preparation

Results

1 Incidence of myopia at age of 18 in the basic sample (n = 539)

According to the number of myopes re-examined and of other cases known to have developed myopia, the incidence of myopia around the age of 18 was found to be 1[illegible] 6% for low birth weighters (n = 302) and 13 1% for full term (n = 237). These percentages represent *minimum* incidences because some myopic cases may have escaped registration in the school medical records. In particular this holds true for those who left school at an early age.

The slightly higher incidence in low birth weighters is due to the 16 cases with myopia of prematurity. Excluding this fraction the incidence of ordinary juvenile myopia is almost similar in the two birth weight groups (12 3 and 13 1% respectively).

Exact incidences for emmetropia and low and high hypermetropia cannot be given. Those re-examined in 1979 (with such refractive values) are so few that they do not necessarily reflect what happened for the many who were not invited for the present follow-up.

2 Refractive change from age of 10 to 18 (n = 137)

In 12[illegible] out of 137 there was a shift towards lower dioptric values (increase in refraction). Seven remained static while only three showed a decrease in refraction (0 25 or 0 5 D).

Table II

Refractive change (towards myopia, in dioptres) from the age of 10 to 18 years. The material is subdivided by birth weight and sex. Mean values standard deviation and range for right eyes only. Mean age at examination is also shown

Sex	Number of persons	Refractive change in dioptres mean ± SD	Refractive change in dioptres range	Mean age in years at exam	
				1970	1979
Low birth weight group					
M	36	1[illegible] ± 1 60	0 – 6 3	10 0	18 3
F	34	1 29 ± 1 03	0 – 4 0	9 8	18 2
Full term control					
M	36	1 26 ± 1 23	−0 2 – 4 3	10	[illegible]
F	31	1 07 ± 0 91	−0 5 – 3 8	10 [illegible]	[illegible]

Table II shows the average change in refraction A division by birth we[illegible] and sex does not disclose subgroups that differ significantly from the rest The results are based on individuals with right eye values only (n = 137) This a[illegible] based on the usually very high correlation between right and left eyes a[illegible] relevant regards to be taken in statistical evaluations (Ederer 1973 Flede[illegible]

The following Tables however do also comprise some left eyes (n = [illegible]) The[illegible] have been included due to significant anisometropia at first exam[illegible] differences are for instance a common feature of myopia of prema[illegible] probably because of varying degrees of damage (by the premature state[illegible] or other extraneous influence) The two eyes are therefore regarded as [illegible] far less dependent than usual and to augment information it is considered fair to employ data from both eyes

Refractive change in refractive subgroups is given in Table III Median [illegible] and 25 75% fractiles show that those with juvenile myopia (at 19/[illegible]) have undergone the most marked changes while emmetropic and hypermet[illegible] have been rather static Myopia of prematurity occupies an intermediate position

The same features are evident from Tables IV and V where all eyes [illegible]

Table III

Refractive change Δ^R (in dioptres) from the age of 10 to 18 [illegible] refractive subgroups (based on 19[illegible] findings) of the two birth [illegible] groups Median value and 25 75 percentiles are shown. 137 right eyes are included – plus some left eyes (n = [illegible]0) deriving from individuals who exposed a significant anisometropia (more than 1 D) when last examined (1[illegible]70)

	Number of eyes	Refractive change Δ^R in dioptres median value	Δ^R fractiles 25% – 75%
Low birth weight group			
Myopia of premat	21	1 2	0 [illegible] – [illegible]1
Juvenile myopia	26	1 [illegible]	1 1 – 3 0
Emmetropia	26	0 [illegible]	0 5 – 1 2
Hypermetropia	11	1 0	0 5 – 1 0
Full term controls			
Juvenile myopia	25	2 5	1 5 – 3 3
Emmetropia	30	0 7	0 5 – 1 0
Hypermetropia	18	0 7	0 – 1 0

Table IV

Association between refractive change (Δ^R from the age of 10 to 18 years) and final (adult) refractive class. Percentage distribution of four Δ^R-classes on myopia (negative refractive values), emmetropia (0 – +0.9 D) and hypermetropia (≥ + 1 D). *Included are the same 157 eyes as in Table III*

	Refractive change (towards myopia) from age of 10 to 18			
	$\Delta^R \leq 0.5$ D n 49	Δ^R 0.6-1.5 n = 61	Δ^R 1.6-2.5 n 24	$\Delta^R > 2.5$ D n = 23
1979 refractive classes				
Myopia	25%	34%	71%	96%
Emmetropia	47%	44%	21%	4%
Hypermetropia	28%	22%	8%	
Total	100%	100%	100%	100%

are however pooled. Further pooling of birth weight groups seems justified from the two former tables which do not indicate significant differences associated with birth weight grouping (except the minor fraction with myopia of prematurity). Refractive changes below 1.5 D predominate in the subgroups of adult emmetropia and hypermetropia. Conversely the more conspicuous refractive changes above 1.5 D) are mainly confined to the myopes.

Table VI shows trends within the group of myopia. In 62% of those with myopia of prematurity (13/21 eyes) there has been only a slight increase in refraction

Table V

Numerical distribution of the four Δ^R-classes (cf. Table IV) on six, more specified refractive groups. Again n = 157 eyes

	Refractive change (towards myopia) from age of 10 to 18			
	$\Delta^R \leq 0.5$ D	Δ^R 0.6–1.5	Δ^R 1.6–2.5	$\Delta^R > 2.5$ D
1979 refractive values				
≥ +3 D	1	6		
1 to +2.9	13	–	2	
0 to +0.9	23	27	5	1
2 to –0.1	7	11	4	
6 to –2.1	3	9	8	18
below –6 D	2	1	5	4

Table VI

Refractive change in myopia of prematurity (left n = 21 eyes) and in ordinary juvenile myopia (according to 1979-findings LBW + FT n = 51 eyes) As in Table IV and V [illegible] right eyes are included except anisometropic eye pairs where both eyes [illegible]

	Refractive change between age of 10 and 18 years in					
	eyes with myopia of prematurity (n = 21)			eyes with ordinary juvenile myopia (n = 51)		
	Δ^R ≤ 0.5 D	Δ^R 0.6–1.5	Δ^R > 1.5	Δ^R ≤ 0.5 D	Δ^R 0.6–1.5	Δ^R > 1.5
Myopic subgroups accord to 1979 refraction values						
−2 to −0.1 D	3			4	11	4
−6 to −2.1 D	2	5	4	1	4	2
below −6 D	2	1	4			5

(below 1.5 D) during adolescence contrasting with 39% (20 51) in juvenile myopia The clear difference between distributions however is not significant [illegible] probably to be explained by the rather small size of the samples.

Finally a short comment on corneal astigmatism as assessed by keratometry The dioptric differences between main corneal meridians ranged from zero to 4 D The mean value was 0.86 D and the median value 0.5 D A change between 1[illegible] and 1979 measurements was virtually absent At least it cannot be stated whether the small differences actually found are due to real alterations or to errors of measurement

Discussion

The age period from 10 to 18 years is interesting also for ophthalmologists

For instance it is within this period that many develop myopia and have to [illegible] with optical obstacles for the first time in life

Considering the otherwise stormy bodily changes around puberty it is, however equally dazzling that a much higher proportion of eyes hardly seem to be altered In fact Sorsby et al (1961 1970) regard the eye as already fully grown around the age of 13 A permanent ocular state should thus be reached rather early while sexual maturation and growth in general are still far from full development.

From an epidemiological point of view eye clinic material has to be disregarded when assessing refractive change during adolescence due to self selection by attendance Most valid information has been obtained from cross sectional studies many of which were briefly reviewed in chapter five of my Thesis (Fledelius 1976)

Several of these suffer from the drawback that they have focused on myopia leaving the important major fraction of children without visual trouble remain unstudied This somewhat neglected part of the refractive spectrum was dealt with recently in cross sectional studies by Johnson et al (1979) and Laatikainen & Erkkila (1980) and also earlier in my own series (Fledelius 1976)

Our present status is in brief the bulk of school children have refractive values between zero and + 2 D and the proportion of myopic cases shows an increase with advancing age This reflects the general trend during adolescence a shift towards lower dioptric values (increase in refraction) The exception is made up by high hypermetropia which is often found to be static

The few published longitudinal studies mainly support this view Hirsch (1952 1961 1964) followed Californian children (Ojai series) from school entry to the age of 14 and Sorsby & Leary (1970) reported on ophthalmic re examinations performed during school age

Using a so-called physiological method of relaxating accommodation (i e without cycloplegic eyedrops) a skewing towards lower refractive values is to be expected in Hirsch s series Accordingly there seems to be too few cases of hypermetropia ≥ + 1 D (39% at school start about 7 5% at the age of 13 14) Further several cases of accommodative pseudomyopia are probably contributing to the high 14 year incidence (18 5%) of low myopia (0 to − 1 D)

Concerning Sorsby s series a certain degree of self selection made the representativity dubious (as claimed by the author himself) For obvious reasons those who need glasses benefit more when volunteering for re-examination this implies a skewing towards (myopic) cases with refractive changes above average

Despite such objections a rough agreement between materials is evident The prototype shows only a small increase (Δ R below 1 25 D) in refraction during school years a minor fraction undergo more marked changes (above 1 25 D 12% in Hirsch series and 28% in Sorsby s apparently skewed sample)

The present material fulfils one of the above requirements that of being examined under cycloplegia on both occasions (after topical cyclopentolate 1% plus tropicamide 1%)

Due to selection criteria however a truly representative follow up picture cannot be given for all 539 who attended for 10 year assessment around 1970 In particular I have only gained incomplete information about those who end up with hypermetropia and emmetropia

The present sample is with purpose even more skewed towards myopia than

that of Sorsby & Leary (1970). However, it is not unreasonable (as [illegible]) refractive changes of the three present 15 year groups (of my [illegible]) and hypermetropia) by and large reflect the true picture in the [illegible] refractive groups of a young adult North western Europe population.

Another question is left unsolved. We do not know exactly when the [illegible] eye becomes static. This would require an interim eye assessment [illegible] age of 15. We just know that some eyes have also shown changes after [illegible] namely developing late juvenile myopia.

Eyes with myopia of prematurity make up a (minor) subgroup show[illegible] of damage (faulty development, Fledelius 1976) connected w[illegible] h the very low [illegible] weight. Estimating from total refractive distribution, however, the low birth [illegible] group does not otherwise seem to deviate from the full term [illegible] controversial question will be further dealt with through analysis of other [illegible] mic parameters in future publications.

Acknowledgment

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References

Ederer F. (1973) Shall we count number of eyes or number of subjects [illegible] *Ophthal (Chicago)* 89: 1–2.

Fledelius H. C. (1976) Prematurity and the eye. Thesis. Ophthalmic follow [illegible] low and normal birth weight. *Acta ophthal (Kbh.)* Suppl. 1[illegible]

Hirsch M. J. (1952) The changes in refraction between the ages of 5 and 14. Theoretical [illegible] practical considerations. *Amer J Optom* 29: 44[illegible]

Hirsch M. J. (1961) A longitudinal study of refractive state of children during the [illegible] years of school. *Amer J Optom* 38: 564–571.

Hirsch M. J. (1964) The longitudinal study in refraction. *Amer J Optom* [illegible]

Johnson G. J., Matthews A. & Perkins E. S. ([illegible]) Survey of ophthalmic conditions [illegible] Labrador community. I. refractive errors. *Brit J Ophthal* [illegible]

Laatikainen L. & Erkkila H. (1980) Ocular findings in school children. *Acta [illegible]* 129–136.

Sorsby A., Benjamin B. & Sheridan M. (1961) Refraction and its components [illegible] of the eye from the age of three. Med. Res. Counc. Spec. Rep. Ser. No. [illegible]

Sorsby A. & Leary G. A. (1970) A longitudinal study of refraction and its components [illegible] growth. Med. Res. Counc. Spec. Rep. Ser. No. 309. London.

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DEMONSTRATION OF A DIFFUSIONAL PATHWAY BETWEEN THE SUBRETINAL SPACE AND THE JUXTAPAPILLARY CONNECTIVE TISSUE

An in Vitro Experiment Using Horseradish Peroxidase as a Tracer

BY

TOR FLAGE and AMUND RINGVOLD

A defect in the blood retina barrier in the optic nerve head region has been demonstrated. In order to show the exact localization of this defect, an in vitro experiment has been performed on rabbit eyes, using horseradish peroxidase as a tracer. From a subretinal depot the tracer diffused between the innermost retinal pigment epithelial cell and the cells of Kuhnt intermediary tissue into the border tissue of Elschnig and the juxtapapillary choroid.
The defect in the permeability barrier is thus located to the junction between the retinal pigment epithelium and the Kuhnt intermediary tissue. The role of the junctional complexes in the Kuhnt intermediary tissue in relation to the blood-retina barrier is discussed.

Key words: blood retina barrier – optic nerve head – subretinal space – retinal detachment – horseradish peroxidase – rabbit eye

After intravenous administration of horseradish peroxidase (HRP) the tracer diffused from the peripapillary choroidal capillaries into the juxtapapillary sensory retina in rabbit and monkey (Flage 1980). This finding demonstrated a defect in the

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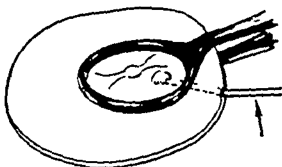


Fig 1

Schematic illustration of the experimental set up A modified chalazion forceps ... in the posterior plate for the optic nerve was used to isolate the central posterior part ... rabbit eye A small subretinal depot of HRP solution was made by careful inj... polyethylene tube (arrow) Following the injection the forceps was tightened ... the tube

blood retina barrier in this region The localization of the defect was supposed ... either in the juxtapapillary retinal pigment epithelium (RPE) in the ... intermediary tissue (KIT) or in the connection between these structures.

The present study was started in order to define the localization of the defect ... the permeability barrier more precisely The problem was tested in an ... experiment by studying the diffusion of HRP from a subretinal depot ... nerve

Material and Methods

Eyes from five adult albino rabbits which were killed with an overdose of ... sodium were used in these experiments The eyes were immediately enucleated ... sterile Ringer solution at room temperature and opened along the equa... chalazion forceps was used to isolate the central part of the posterior eye ... diameter of the ring on the forceps was 10 mm and in the solid plate a hole ... 3 5 mm was made for the optic nerve By careful dissection from the equator ... polyethylene tube (Intramedic Clay Adams outer diameter 1 ... mm) was ... subretinal space The tube was connected to a ... syringe with a ... outer diameter 0 ?7 mm) fitting into its open... Ringer solution was carefully injected to raise ... diameter) around the end of the tube Great

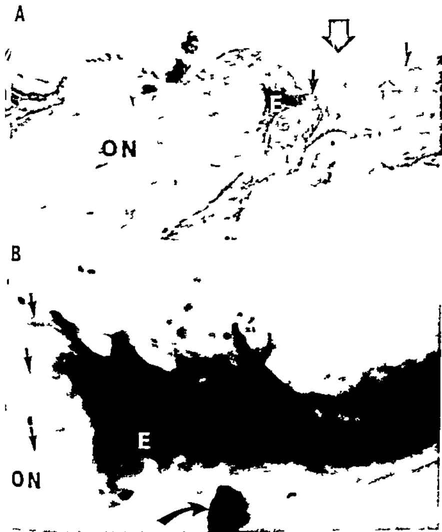


Fig. 2A

stained cryostate section of the ONH region. The peripapillary retina does not show any [illegible] of detachment. Black staining indicates HRP activity. The peripapillary area facing the [illegible] depot (broad arrow) shows distinct staining located in the outer part of the sensory [illegible] (small arrows), the anterior part of the border tissue of Elschnig (E), and the [illegible] peripapillary choroid (arched arrow). The HRP activity in the choroid disappears rapidly [illegible] from the ONH. Open arrow points to unstained choroid. The outer retinal layers on the [illegible] side of the ONH show faint staining. Black staining [illegible] present both in the OHN and in all parts of the choroid. Optic nerve (ON) × 40

Fig. 2B

[illegible] from Fig. 2A. From the anterior part of the border tissue of Elschnig (E) strands of [illegible] tissue [illegible] HRP activity project into the adjacent optic nerve (ON) (small [illegible]). Arched [illegible] points to vessel lined with erythrocytes giving pseudo-peroxidase [illegible]

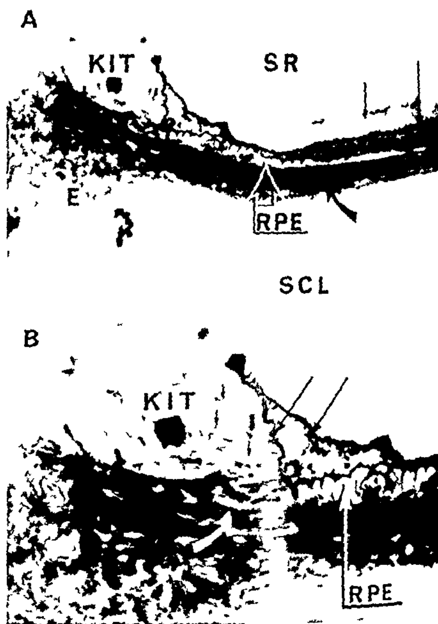


Fig. 34

Unstained light microscopic section from epon embedded tissue. HRP in the [illegible] (SR) is to a large extent located to the rod cone layer (long arrow) while [illegible] substance have penetrated the outer limiting membrane and reached a level [illegible] outer nuclear layer and outer plexiform layer (small arrow). The retinal pigment epithelium (RPE) is unstained by the tracer (open arrow) while the anterior part of the border [illegible] Elschnig (E) and the juxtapapillary choroid (arched arrow) are distinctly stained [illegible] intermediary tissue (KIT). Sclera (SCL) × [illegible]

wards the optic nerve head (ONH) Following the injection the fo ceps was htl ghtened to close and mmob l ze the tube The complete prepara n wa kep rved n the Ringer solution at room temperature during the mount ng nject p e urc and for a arying d ffus on time for the tracer follow ng the njection D ff n re ne ns l e me from the njection of the tracer unt l the preparation was immersed n l e t e At he end of this time the whole preparation w th the tube and the forceps n p e w s n d ce-cooled glutaraldehyde fixative (2 5% in 0 1 M phosphate buffer pH 4 Tl e t n ions of d ffus on times and tracer solut on concen ra o c l 3 5% the times ranging from 10 to 30 m n and 1% solut o l
fter glutaraldeh de fixation for 17 h the tissues were washed h l a e (pH 7 4) w th 5% sucrose before be ng cut on a freez ng n 0 0 µm th k The sections were ncubated n tris HCl buffer d 1 O solution (pH 7 6) for 45 m n Some of the th n sect ons were mo c and xamined w thout further stain ng The rest of the sections e h 0 1 M phosphate buffer) deh drated in graded ethanols and e n L l icroscop c sections of about 1µm th ckness were exam ned e h n th toluidine blue The ultrath n sect ons were made w th an LKB ned a Siemens Elmiskop 1A e ther unsta ned or after s a n ng l l ne ead.

Results

ght microscopy of unstained cryostate sections did xtrapapillary retinal detachment (Fig 2A) The juxtapap llar n f tracer showed distinct staining indicating HRP actı p rticul part of Elschn g border tissue but also in the adjace t l oro etinal layers A striking feature was that the HRP actı t in d rap dly away from the ONH while the stain ng of the retin tracer depot. Strands of HRP stained connective uss e pr heavily stained anterior part of Elschnig border tissue into the adja e e (Fig 9B) On that side of the ONH opposite to the depot, the outer re ers always revealed only faint staining and the choro d did not show extrava lar HRP at all. The inner part of the sensory retina did not show HRP actı ty in an region Staining due to intravascular erythrocytes was present both in the optic nerve head and in all parts of the choro d

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F g 3B

Detail from Fig 3A Long arrows po nt to HRP n the juxtapapillary subretinal space In the adjacent MT thin lines of HRP actı ity are seen (small arrows) That part of Bruch membrane continu ng towards the optic nerve beyond the junction between the RPE and the MT arched arrow) is hea ily stained The juxtapapillary RPE-cells are unstained by the tracer × 560

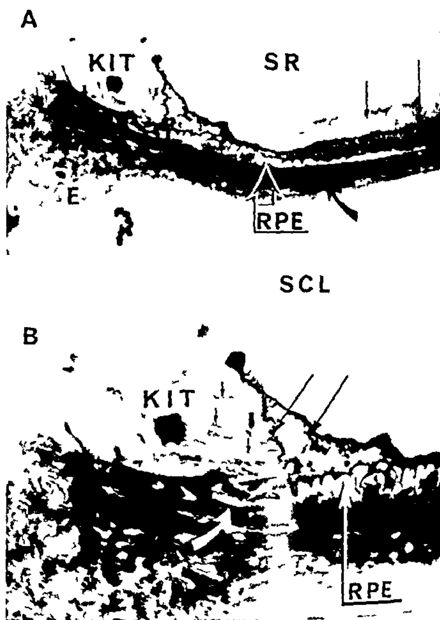


Fig 34

Unstained light microscopic section from epon embedded tissue. HRP in the sensory r
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(RPE) is unstained by the tracer (open arrow) while the anterior part of the border tis
Elschnig(E) and the juxtapapillary choroid (arched arrow) are distinctly stained. K
intermediary tissue (KIT). Sclera (SCL). × 200

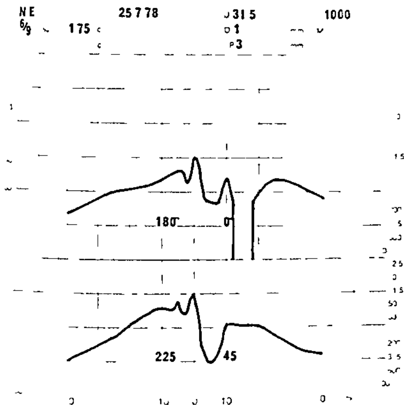


Fig 4

tatic perimetry profiles recorded in Case NE with active central serous retinopathy Above lotted on the horizontal meridian Below on the axis passing through the site of focal breakdown of the choroido-retinal barrier and the fovea

ery case on the 180–0 axis and although the density of the defects varied from dividual to individual these were always found to be larger and deeper when the us selected for investigation corresponded to that joining the site of focal horoido-retinal barrier disturbances to the fovea (Fig 4) As the serous fluid sorbed paracentral scotomata became smaller and foveal sensitivity recovered in l cases (Fig 5)

After the detachment had settled 10 of the 14 patients with a recently active ntral serous retinopathy and 7 of the 13 cases with resolved central serous tinopathy of longer duration were noted to have needle shaped scotomata in the racentral region Scotomata varied between 1 and 3 in width and from a slight pression on static profile to quite dense cuts which approached the baseline of the atic chart

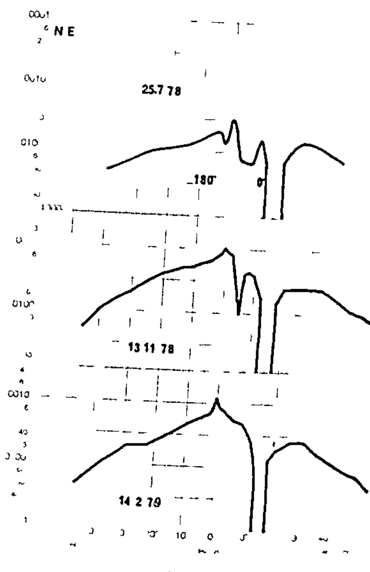


Fig 5
Recovery pattern of static perimetry profile of case NE over a period of *s* mo

In 11 of these cases residual paracentral scotomata were detected on th axis However 6 others showed no abnormality on this meridian but suc became clearly evident if the static profiles were performed on the axis p site of the now sealed breach in the choroido-retinal barrier to the fovea

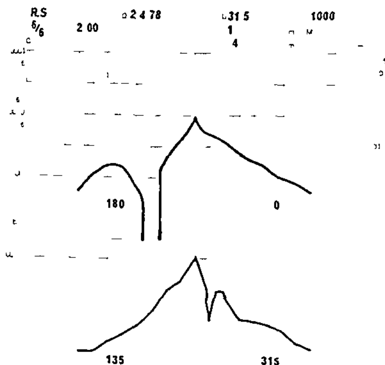


Fig 6
...tic perimetry profile recorded 6 months after the onset of symptoms Case RS Normal ...ield plotted on 180 −0 axis Residual paracentral depression present at 135 −315 axis

...us needle shaped scotomata were found in 63% of cases with resolved idiopathic ...tral serous retinopathy

The time taken for the serous fluid to absorb in the cases of central serous ...nopathy examined in this study ranged from 2 to 11 months with a mean of 4 ...nths Of the 11 patients in whom detachments were observed to have resolved in ... than 4 months 6 drew defects on Amsler grid and 3 of these noted to have ...ic perimetric defects

...n 16 patients whose detachments took 4 months or more to settle all 16 ...erved distortions on the Amsler grid tests and 14 retained abnormal static ...imetric profiles No patients were found to have residual changes on static ...imetric examination who did not record defects on Amsler charting

Discussion

The results of this study clearly indicate that Amsler testing, which can be carried out quickly without recourse to any special technical expertise, is as good as static perimetry for evaluating central field disturbances in the acute phase of idiopathic central serous retinopathy and in some ways superior to static perimetry in assessing the incidence of residual central field defects since 81% of patients continued to plot distortions on the Amsler grid as opposed to 63% who retained clearly abnormal static perimetric profiles. The percentage of patients who continued to draw defects on the Amsler grid examined in our study was similar to that reported by Klein et al (1974) who found that 89% of their patients recorded changes. The higher number of patients who drew disturbances on the Amsler chart may well arise since it is possible by this method to plot changes associated with micropsia and metamorphopsia. Thus it would appear that the two forms of examination do not provide exactly comparable information about retinal function in patients who have developed a central serous retinopathy after the serous fluid has absorbed, since static perimetry testing detects predominantly the paracentral lesions whereas Amsler charting often indicates more widespread changes at the posterior pole.

The greatest depression on static perimetric profiles was found not to coincide with the point at which a breakdown of the choroido-retinal barrier developed in the acute phase, a site which might be considered likely to show disturbances of retinal function, but was invariably located paracentrally and most apparent in the axis which joined the leaking point to fixation. It would seem probable therefore on the basis of these findings and the shape of the scotoma detected on the Amsler chart in the acute phase that fluid accumulating in the space created between the pigment epithelium and the neural layers immediately over the break in the choroido-retinal barrier tracks towards fixation and that part of the retinal disturbances are caused by persistent malfunction of elements within the macular area.

Hache et al (1972) thought that the incidence of residual defects of retinal function in patients who had acquired a central serous retinopathy depended on how quickly the fluid absorbed. The results of this study confirmed this impression as disturbances of the static visual fields were found in 27% of patients where the serous fluid cleared in less than 4 months but rose to 85% in cases in which the apposition of the neural layers of the retina to the pigment epithelium was delayed beyond that time. As Chisholm et al (1975) showed that the level of recovery of central visual function in patients with successfully treated rhegmatogenous detachments involving the macula is related to the duration of retinal separation, it would appear that similar but more subtle changes develop predominantly in ...

... and remain as a permanent feature in the ma... ... ...ave ... central serous retinopathy. Support ... ... provided by the observations of Kroll & Machemer (1... who ... ... experimental studies, reported that cone outer segments appeared ... ...ess ... than their rod counterparts when experimentally ... ... primates were reattached, and by the fact that patients with ... ... retinopathy continue to score poorly on the Farnsworth M... ... ... (Bonnet 1976, Leaver & Williams 19...).

Although in the majority of patients who have developed ... central serous retinopathy the residual field changes cause little ... ... requiring a high level of central visual function, e.g. those ... ... photographic or micro-engineering industries may remain permanently handicapped in the execution of their work, and this study indicates some ... the reasons as to why for these the disease process is not as benign as has previously been ...

Acknowledgements

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References

... L. A., McClure E. & F... W. S. (19...) Functional recovery of the retina after ... detachment. Trans. Ophthal. Soc. U.K. ... 167-178.
... J. & Bonnet M. (1976) La Macula, p. 97. Masson, Paris.
Labe J. C., Constantinides G. & Turut P. (1979) Les aspects évolutifs de la ... séreuse centrale. Bull. Soc. franç. Ophtal. ... 25...
Leaver P. K. & Williams C. M. (1979) Argon Laser photocoagulation in the treatment of central serous retinopathy. Brit. J. Ophthal. ... 674-677.
... M. L., Van Buskirk M., Friedmann E., Gragoudas E. & Chandra S. (19...) Experience with non-treatment of central serous retinopathy. Arch. Ophthal. Chicago ... 1...
... J. & Oosterhuis J. A. (19...) Pigment epithelium in serous ... in central serous detachment of sensory epithelium. Docum. Ophthal. ... 1...
... A. J. & Machemer R. (1969) Experimental retinal detachment and re-attachment in the Rhesus monkey. Electron microscopic comparison of rods and cones. Amer. J. Ophthal. 6...
...
...rhoum I. (1969) Central serous retinitis (a follow-up study). Acta Ophthal. ...
...
...ke R. C., Burton T. C. & Leaverton P. E. (1974) Ruby laser therapy of central serous retinopathy. Trans. Amer. Acad. Ophthal. Otolaryng. ... 9...

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COMPUTERIZED VISUAL FIELD SCREENING IN THE MANAGEMENT OF PATIENTS WITH OCULAR HYPERTENSION

BY

KJELL DYSTER AAS ANDERS HEIJL and LEIF LUNDQVIST

Visual field testing with the Competer fully automatic computerized perimeter (Heijl & Krakau 1975) employing a supra liminal screening test procedure was used in a material of 1013 eyes with ocular hypertension in which earlier routine perimetry (kinetic and static) on the Goldmann perimeter had yielded a normal result The automatic screening was repeated if positive and manual control perimetry was used in order to confirm or reject identified field defects This procedure revealed field defects that could be confirmed at both automatic and manual perimetry in 3 6% of the eyes In a control group the incidence of field defects found at manual perimetry during the same time interval was calculated at 0 4% Thus automatic screening revealed several times more field defects than manual routine perimetry Eyes in which repeated automatic screening had indicated defects which manual control perimetry failed to confirm showed a high percentage of field loss at later follow up The results are discussed and the conclusion is drawn that automatic screening is clearly superior to manual routine perimetry used at present The most practical solution in many eye departments would be to use a computerized perimeter for the visual field screening of glaucoma suspects

Key words visual field screening – automatic perimetry – computerized perimetry – ocular hypertension – glaucoma

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The disclosure of a glaucomatous visual field defect in an eye with increased intraocular pressure immediately leads to a re-classification of the eye. It can no longer be labelled a hypertensive eye but has to be classified as a glaucomatous eye. This involves different management, maybe even surgery. The examination of the visual field can be considered the crucial part in the management of ocular hypertension. The task of checking the fields of such patients is difficult in several respects. First we are dealing with a very large number of patients, secondly the role of the perimetrist is not made any easier by the knowledge that all previous fields in the eye have been normal and that in ocular hypertension the likelihood that field defects may develop is small (Armaly 1979, Nelleman Sørensen, Nielsen & Norskov 1978, Linner 1976, Kitazawa et al. 1977, Perkins 1973). In such cases it might be an advantage if the field screening could be handled by an automatic perimeter. Much time and and effort could be saved in such a way. There are indeed data available which indicate that automatic perimetry might work just as well as conventional manual perimetry in the detection of glaucomatous field loss (e.g. Heijl 1976, Heijl et al. 1980, Aulhorn & Durst 1977, Keltner et al. 1979). However, one might go even further and suspect that in fact automatic screening perimetry might be superior to routine manual perimetry, as it is usually performed in the detection of field defects in this group of eyes. A few earlier studies (e.g. Heijl 1976, Spahr et al. 1978) indicated that this might be true.

The purpose of this study was to analyse the results of the application of an automatic perimeter (the Competer) (Heijl & Krakau 1975) to a large material of eyes with increased intraocular pressure but normal fields, i.e. eyes with ocular hypertension. We suspected that many field defects had been overlooked in these eyes.

Material

Two groups of patients were studied.

a) A test group of 1013 eyes in 541 consecutive patients. All these eyes were classified as ocular hypertensives. They showed or had shown elevated intraocular pressure (≥ 22 mm Hg) but normal fields at earlier routine kinetic perimetry on the Goldmann perimeter. The average time that had passed since the previous manual perimetry was 11.5 months (± SD 4.6 months).

b) A control group of another 201 eyes in 115 patients. Also these eyes had ocular hypertension.

The average ages of the patients in groups a and b were 66 years (range 20-93 years) and 64 years (range 31-88 years), respectively.

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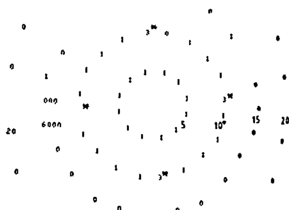


Fig 1

Computer print-out of a normal test result The test result at each of the 64 test points printed out numerically The table (top left) contains the frequency distribution of the result of the 64 points The left column shows the stimulus intensity number A high number means a higher sensitivity Intensity level 0 denotes no response to the maximum stimulus 9 a fairly low threshold The right column indicates the number of the 64 points tested whose test results had the varying intensity levels The Q value (6 here) is the most common value Test points with a threshold equal to Q are printed out as 0 in the graphic display All points with a higher threshold are printed out as negative numbers and zeros added to negative numbers < −1 in order to make them stand out more clearly graphically e g −6000 in the blind spot (compare Krakau 1978) Actual threshold determinations have been performed only at the initial four test points (marked in the print-out) and at missed points (in the blind spot)

Methods

Automatic perimetry

Perimeter

The test group was subjected to automatic screening perimetry on the Competer automatic perimeter

The Competer perimeter (Heijl & Krakau 1975) is a fully automatic computerized perimeter It has 64 static test points (light emitting diodes) concentrated in the central visual field from 5 to 20 from fixation (Fig 1) The light emitting diodes can be lit at 16 intensity levels the ratio between two consecutive levels being 2 1 The test result is displayed by a printer as illustrated in Fig 1

Throughout the study we used 0 5 sec stimulus presentation time an interstimulus interval of 2 0 sec and a background illumination of 1 0 or sometimes 0 1 cd/m²

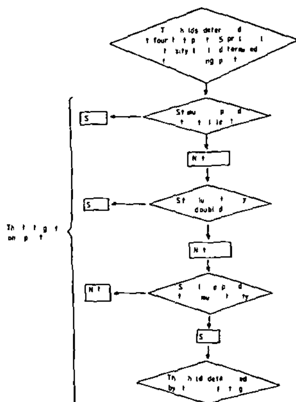


Fig 2

Test logic (simplified) All points are tested in random sequence The figure shows the testing at *one* point

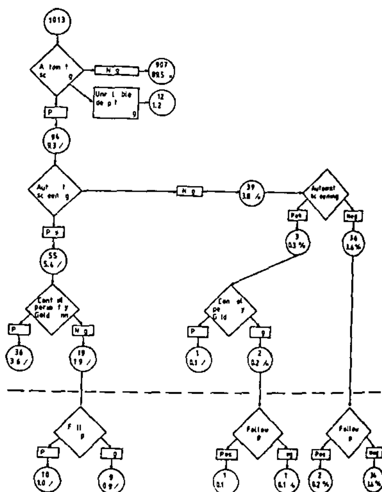


Fig 3
Flow diagram of study design (see methods and results)

Test logic

The test logic governing the test procedure was almost identical with the described by Heijl 1976 It is a screening test logic employing mainly supra l stimuli Its main features appear from Fig 2 Test time is 3-4 min per eye

Interpretation

The interpretation of the automatic fields followed the criteria stated by H 1976 Thus a visual field was considered normal if all points (outside the blin area) ended on a sensitivity level not more than one intensity level lower th first intensity level at which it was exposed (c f Fig 1) One single test poin outside the blind spot area with a lower sensitivity than that was enough to c an automatic field chart as abnormal In the Competer the patient s fixat

checked by the presentation at random intervals of stimuli in the blind spot area of the eye tested Among these stimuli the number that has been perceived is divided by the total number of exposed stimuli This quotient is denoted the fixation quotient. Automatic fields with a fixation quotient ≥ 0 25 were labelled unreliable and the test was repeated If the fixation quotient at the repeated automatic screening was still ≧ 0 25 no further automatic perimetry was performed and the eye was excluded from the study (Fig 3) Another criterion that had to be fulfilled for a test to be regarded as reliable was that the blind spot had to be present in the automatic chart Otherwise the test was repeated just as in the case of a high fixation quotient.

Manual perimetry

Procedure

The manual fields were plotted with a combined static and kinetic procedure At least two isopters were plotted one peripheral and one as close to the 25 circle as possible The central field from 2 5 to 15 was then tested statically with the same object as that of the 25 isopter in about 20 static spot checks

Interpretation of Goldmann fields

The interpretation of the manual kinetic fields was done in the conventional manner Nasal steps arcuate lesions and paracentral scotomas were all considered abnormal as was any distinct deviation of an isopter from its expected course An isolated enlargement of the blind spot or a baring of the blind spot with no other concomitant plottable defect was not taken as a sign of abnormality

Final classification of eyes tested on the automatic perimeter

The classification of the eyes subjected to automatic perimetry is illustrated in Fig 3 A combination of repeated automatic screening and manual control perimetry was used in order to confirm or reject defects found at the primary automatic screening of the 1013 eyes involved Eyes with a *normal* test result at the initial automatic screening were not examined further Eyes with an *abnormal* result at first screening were subjected to a second automatic test If at this second screening a defect was found in the same area as in the first screening the eye was denoted as having a field defect confirmed at automatic perimetry This required that the first and the second test showed at least one common abnormal test point or that neighbouring points were abnormal in the first and second screening respectively If this condition was fulfilled the eye which had thus demonstrated a field defect confirmed by automatic perimetry was subjected to manual control perimetry (Fig 3) If this condition was *not* fulfilled a third automatic screening was performed the result of which determined whether manual control perimetry should be carried out (c f Fig 3)

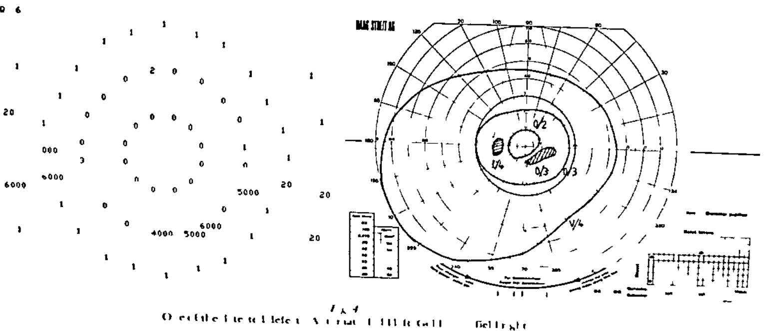


Fig 4

Control group

Since in the study group (a in Material) automatic screening was not performed at the same time as the routine perimetry on the Goldmann perimeter but on an average 11 5 months later we had to estimate the normal incidence of glaucomatous field loss in our material of ocular hypertensives when routine manual perimetry was performed Automatic screening has come to be the routine method at our glaucoma unit for the screening of suspect glaucomatous field since it introduction in 1977 Therefore we did a retrospective study of 201 consecutive eyes with ocular hypertension which in 1974 had shown a normal result at routine kinetic perimetry The result of the subsequent routine manual field test in these eyes was checked

Results

Test group

Fifty five eyes (5 4%) showed an abnormal result at the two initial automatic screenings Out of these 36 (3 6%) could be confirmed as pathological at manual control perimetry (field defects confirmed at automatic *and* manual perimetry) while in 19 no defects could be found at manual control perimetry These latter 19 eyes thus represented the tentative false positives (1 9%) after automatic screening performed twice However in this group more than half (10 eyes – 1 0%) showed reproducible field defects at later follow up in the same area as that indicated by the initial automatic screenings (Fig 3 and Discussion)

There were 39 eyes (3 8%) where an initial positive automatic screening was followed by a negative automatic rescreening Among these eyes three were positive at a third automatic screening two of which later proved to have field defects (Fig 3) Thirty six eyes were negative at this third automatic screening Only two of these showed field defects on later follow up

Control group

One out of the 201 eyes with normal fields at routine manual perimetry with the Goldmann perimeter in 1974 showed field defects at the next field test. The average time between these two tests was 14 2 months (± SD 4 4 months) When the routine perimetry was used this gave an incidence of field defects in our material of 0 5% in 14 2 months or 0 4% in the 11 5 months which was the average time interval between the manual routine perimetry and the initial automatic screening in the study group

Discussion

If we subtract the incidence of field defects in the control group fro[m the] percentage of identified previously unknown field defects confirmed at auto[matic] *and* manual perimetry in the test group (3 6−0 4%) we arrive at the figure [...] This represents a conservative approximation of the number of abnormal fiel[ds ...] would have been missed by routine manual perimetry as described before [...] this figure is too low for at least two reasons First the assumption that auto[matic] screening identifies *all* defects is not correct (e g Heijl et al 1980) This is val[id for] all perimetric techniques Secondly it seems quite clear that many of the eye[s with] field defects confirmed at automatic but not at manual control perimetry real[ly had] true field defects at this time since 53% (10 out of 19) at follow up 1 2 year[s ...] showed field defects in the area indicated by the first automatic screening [...] defects were usually confirmed at automatic perimetry and were also fou[nd at] manual perimetry in those cases in which this was performed We then arri[ve at a] figure of 4 6% detected fresh defects This is a high figure considering the fa[ct that] the incidence of field defects in the material studied should be small – [ocular] hypertension is much more common than glaucoma with field defects Certa[inly this] figure is influenced to a certain degree by the fact that a small part (< 5%) [of the] material was second eyes in patients with established glaucoma in the other e[ye. In] the control group however this percentage of second eyes was somewhat [higher] and the observed incidence at manual perimetry still only 0 5%

Automatic perimetry thus revealed several times more field defects than [were] observed in the control group while the incidence in the control group was in good agreement with published figures (e g Perkins 1973 Linner 1976 Nel[son-]Sørensen et al 1978)

The high percentage of newly detected field defects when the automatic [...] was applied most certainly indicates that many *early* glaucomatous defects ha[ve been] overlooked at the manual routine screening Sooner or later the manual [...] would also have spotted the defects which however might be overlooked for [...] years while still small and difficult to detect The automatic test often ide[ntifies] small paracentral scotomas which are easy to miss at traditional perimetry [...] result is in accordance with those of Heijl (1976) who found that a [...] automatic screening revealed a large number of previously unknown field [...] in a material of ocular hypertensives and patients with small to medium glaucomatous field defects These defects were confirmed at conventional [...] and static profile perimetry

It must be emphasized however that the results of this study do *not* warra[nt] conclusions as to the superiority of automatic perimetry as a whole over [manual] perimetry as a whole The only comparison that is made is between *rou[tine]* [...]

perimetry as described above and automatic screening on the Competer In fact the previous study by Heijl (1976) has shown that manual Armaly screening performed under optimized conditions gives results very similar to those of Competer screening Another study (Heijl et al 1980) shows that the Competer with a threshold measuring test logic works about as well for the detection of defects as an experienced and well trained technician using meticulous combined static profile and kinetic testing with the Tubingen perimeter and both methods miss a few subtle defects The explanation of the differences observed in the present study is thus not due to a level of perfection in the automatic perimeter which is unattainable at manual perimetry but rather to the fact that routine manual perimetry which is still the major method employed in spotting field loss in suspect glaucoma is unfortunately not very often performed according to those exacting standards which are necessary for a reliable result One of the many obstacles which prevent the disclosure of early glaucomatous field loss is the non randomized quite predictable stimulus sequence which is normally used at manual perimetry (Heijl & Krakau 1977)

The number of false positives in the first automatic screening of this study is smaller than previously observed This might at least in part be due to the fairly strict criteria that were used in this study to designate an automatic field as reliable Only few of these 39 eyes showed field loss later (Fig 3) This shows that automatic screening repeated once provides a quite good separation between normal and abnormal fields Most false positive fields fell into a quite distinct pattern with isolated missed points located above the blind spot upwards on the 15 circle and at 20 from fixation

The fact that the group of field defects confirmed at automatic but not at manual perimetry later proved to contain many cases of early reproducible glaucomatous field loss shows that manual perimetry might easily fails to reveal early glaucoma tous defects even if it is performed in a directed fashion – at least if static profile perimetry is not part of the strategy The same observation has been made before Some cases denoted as false positives in one study (Heijl 1976) – since they could not be confirmed at manual perimetry – later appeared in exactly the region that had been indicated by the initial automatic screening (Heijl 1977)

Conclusion

The conclusion which emerges is that automatic screening on the Competer is clearly superior to *routine* manual perimetry as described above for the detection of glaucomatous field defects We have no reason to believe that this routine manual perimetry is of a lower standard than that performed in the majority of eye departments It should also be possible to arrive at similar results with other

Most authors agree that the pathogenesis of glaucoma damage of the optic nerve is related to the balance between local blood pressure and IOP (Hayreh 19... The *visual evoked response* (VER) is sensitive to many types of optic nerve affections and indeed several reports have delt with VER abnormalities in well-established cases of OAG (Ermers et al 1974 Cappin & Nissim 1975 Bartl 1978 Huber & W... 1978)

This paper briefly presents the results of an investigation of the VER in a sample of persons with long term observation of untreated intraocular hypertension. The effect of a 15 20 mmHg artificial IOP increase is evaluated. All parameters are judged by means of a normal sample (n = 52 1% significance level) and the diagnostic and prognostic perspectives are discussed

Material and Method

Six men and three women (median age 51 years (32 67)) with a median period of observation of 5 years (2 9) were examined. They had been followed twice a year with examinations including photography of the optic discs and extended field analyses. The IOP's were concentrated in the 22 30 mmHg region and the values of the central corneal thickness did not in any case motivate a correction of the applanatory readings (Ehlers et al. 19... The corrected visual acuity was at least 6/9 and there were no complicating eye or brain diseases.

The VER was recorded from midline occipital and right mastoid electrodes. The central 30 × 22 of the retina were stimulated with a TV generated black and white reversing chequerboard. Large checks (110) with a 0 95 contrast level were used. Transient VERs were obtained with 3 75 shifts/s and steady state VERs with 15 and 30 shifts/s respectively. Transient VERs were measured before and after application of a Müller spring dynamometer to the sclera bringing about an IOP increase of 15-20 mmHg ... In the normal sample resulted in a significant drop in VER amplitude without any change in latency. The steady state responses were evaluated with respect to correct representation of the stimulating frequency increase of the IOP had no effect on these VERs in the normal sample

Results and Discussion

Two persons a women aged 59 years and a 32 year-old man showed normal transient VERs with the habitual pressure level but elevation of the IOP resulted in amplitude drops well outside the normal range the latencies remained normal. The steady state responses were unchanged by pressure loading. The anatomy of the chamber angle was considered normal at most investigations but one other

found that a slight mesodermal dysgenesis was possible in the first patient and that discrete signs of bilateral angle contusion could not be excluded in the second patient Diurnal pressures varied between 22 and 29 mmHg in both cases

It is tempting to interpretate the VER response in these two cases as an increased pressure susceptibility of the optic nerve However such a conclusion obviously demands a considerably longer period of follow up

Another patient a man aged 66 years had been followed for five years with pressure levels of 22 28 mmHg in his only eye the other having been lost from trauma The optic nerve head presented a large circular excavation without any vessel displacement or atrophy the c/d ratio had constantly been 0 8 The initial transient VER showed gross deformation not allowing any precise latency and amplitude measurements IOP elevation did not change the pattern appreciably The steady state responses were normal Reduction of the IOP to 12 mmHg by means of timolol maleate 0 5% twice a day did not normalize the VER.

This outcome suggests a damaged optic nerve but whether this is due to a static possibly congenital defect or to incipient pressure changes can only be determined by further observation

Another male 67 years of age had developed a frank OAG in his right eye since the last control examination without any signs of the same condition as yet from the other The transient VER s however were grossly deformed from *both* eyes before IOP increase whereas the steady state responses were normal With the usual bilaterality of OAG in mind the present findings point at a high degree of sensitivity of the presently employed VER technique in early detection of glaucomatous lesions of the optic nerve

In Bartl investigation (1978) artificial IOP encrease and VER were studied in normal and glaucomatous eyes However the pressure level had to be above the ophthalmic diastolic pressure before any VER changes were recordable Possibly this is explained by the use of smaller checks of lower contrast and a smaller retinal stimulation area Furthermore the pattern was shifted with a 5 Hz frequency (10 shifts s) which means that the response in all probability is a steady state VER and such were found to be unchanged also in the present investigation

A more detailed description of the VER technique employed and analyses of normal and pathological samples are under preparation

Acknowledgment

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References

Bartl C (1978) Das Elektroretinogram und das evozierte Sehrindenpotential bei normalen und an Glaukom erkrankten Augen Albrecht v Graefes Arch klin exp Ophthal 243–269

Cappin J M & Nissim S (1975) Visual evoked responses in the assessment of field defects in glaucoma Arch Ophthal (Chicago) 93 9–18

Ehlers N Bramsen T & Sperling S (1975) Applanation tonometry and central corneal thickness Acta ophthal (Kbh) 53 34–43

Frmers H J M Heer J de & Lith C H M van (1974) VECPS in patients with glaucoma In Dodt E & Pearlman J T (Eds) Docum Ophthal Proc Series 4 Dr W Junk Ha

Hayreh S S (1978) Pathogenesis of optic nerve damage and visual field defects In Heilmann K & Richardson K T (Eds) Glaucoma Conceptions of a Disease Georg Thieme Stuttgart

Huber C & Wagner T (1978) Electrophysiological evidence for glaucomatous lesions in the optic nerve Ophthal Res 10 22–29

Kolker A E & Hetherington J Jr (1976) Becker Shaffer's Diagnosis and Therapy of the Glaucomas The C V Mosby Company Saint Louis

Nørskov K (1970) Glaucoma screening Acta ophthal (Kbh) 48 418–433

Roth J A (1974) Inadequate diagnostic value of the water-drinking test Brit J Ophthal 55–61

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PRACTICAL PROBLEMS IN THE USE OF OCUSERT® PILOCARPINE DELIVERY SYSTEM

BY

PENTTI SIHVOLA and TUOMO PUUSTJÄRVI

The effects of the long acting pilocarpine preparation Ocusert® were studied by its application for one week into a total of 59 eyes of 42 earlier untreated glaucoma patients From the diurnal pressure curves it was found to be equivalent to three daily administrations of 2 or 4% p locarpine topically the experiences were as follow 8 of the preparations had to be removed before the end of the experiment due to insufficient effect and two were removed for other reasons 19 fell out accidentally 3 were displaced so as to be visible occasionally under the eyelid but did not fall out, 2 patients succeeded in replacing the preparation after it had fallen out In the 19 eyes (37%) of all patients still in the trial after the first day the preparations stayed in place without any difficulty for the whole week All patients experienced minor side-effects but only one of them terminated the treatment due to these side-effects Serious side-effects did not occur

Key words ocusert – pilocarpine therapy long acting pilocarpine preparation – glaucoma management

One major problem in the treatment of chronic glaucoma is the high pressure values measured in many out patient departments When the patient is taken into the hospital ward for checking the effectiveness of the medication it is possible to obtain a very satisfactory diurnal curve with what have had been reported to be an unsuccessful medication programme One reason for this may be the reluctance to apply evedrops several times daily to an eye which is completely without subjective symptoms In addition old people living alone often have difficulties in applying evedrops

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For patients with arm or hand injuries and for old and demented pa[illegible] especially out patients the Ocusert pilocarpine delivery system would seem [illegible] However both Heilman (1975a) and Hennig (1976) reported considerable d[illegible] ties in the Ocusert treatment one of the greatest was the problem of ma[illegible] the Ocusert device properly in the conjunctival cul-de sac

In this study we have attempted to clarify whether Ocusert P-40® is s[illegible] routine use in certain patient groups

Material and Methods

The material consisted of 52 eyes from 42 patients with untreated glauco[illegible] randomly chosen from the ophthalmology ward of the University Central Hos[illegible] of Kuopio They consisted of 27 woman and 15 men The age of the women ra[illegible] from 44 to 82 average 67 years The men ranged from 30 to 80 years with [illegible] average of 64

All the patients were examined with the normal routine glaucoma tests vis[illegible] acuity slit lamp biomicroscopy gonioscopy applanation pressure ophth[illegible] moscopy Goldmann visual fields and diurnal pressure curves. The diagnosis [illegible] based on following criteria intraocular pressure equal to or greater than 23 mm[illegible] measured by Goldmann applanation and glaucomatous cupping of the optic d[illegible] with or without defects in the visual field After confirming the diagnosis, a furthe[illegible] diurnal pressure curve was drawn after administration of three doses of pilocarp[illegible] 2% Unless the results were satisfactory (all readings of pressure under 23) a ne[illegible] curve was constructed after three doses of pilocarpine 4%

After completion of these tests Ocusert P-40® the dimensions of which ar[illegible] 5.5 × 13 × 0.5 mm was placed in the upper (or sometimes lower) cul-de-sac of th[illegible] eye A new diurnal pressure curve was drawn with Ocusert in place If this curv[illegible] proved clinically satisfactory then after confirming that Ocusert was still in plac[illegible] the patient was allowed to return home After 7 days the patient returned t[illegible] hospital for interview and a further diurnal curve was made If Ocusert had fa[illegible] out the trial was terminated In 5 cross-over patients Ocusert was for the fir[illegible] week placed in the right eye and pilocarpine eye-drops in the left eye 3 times dai[illegible] For the second week this scheme was reversed

Results

The 52 eyes included in this trial were diagnosed as follows glaucoma simplex 21 cases glaucoma capsulare 24 cases glaucoma congestivum chronicum 6 cases and glaucoma juvenile one case

Two or 4% pilocarpine was effective in all cases with the exception of seven cases of glaucoma capsulare and one of glaucoma congestivum chronicum Ocusert was not effective in these exceptional cases and was removed after the first day

Two patients from the group voluntarily terminated the trial one for mental reasons and the other the 30-year-old glaucoma juvenile patient experienced so much pain from Ocusert that he wished the trial to be stopped This patient experienced similar pain after 2% pilocarpine

In all cases where pilocarpine gave a clinically satisfactory diurnal pressure curve an equivalent curve was obtained with Ocusert P-40® and was still obtained on the seventh day

Of the total amount of Ocusert (52) 19 preparations (37%) had fallen out after one week 3 had been some partly extended from the eyelids but the patients had succeeded in replacing them and 2 had fallen on to the hand or slipped onto the cheek and again the patient had succeeded in re inserting them Seven units of preparations had distorted forming a figure 8 in the cul-de-sac. Nineteen units (37%) remained in place without difficulty for the whole week. Conjunctivitis or objective symptoms or irritation were not apparent. The average age of the patients in whom Ocusert did not remain in place was 70 years Only one of these had structurally a low cul-de sac Other eyelid anomalies or apparent weaknesses in the eyelid were not present

Only one of the patients made any spontaneous complaint about Ocusert but during the interview all patients complained about irritation during the initial days and 3 had felt a foreign body sensation at the beginning and had noticed some reddening of the eye

Discussion

Further interest was generated when it was shown that Ocusert caused considerably less accommodation myopia than the equivalent pilocarpine drops (Heilmann 1975a Leydhecker 1975) In young healthy students four doses of pilocarpine 2% caused up to 10 D myopia whereas Ocusert caused under half of this amount In this study the only glaucoma juvenile patient suffered pain explained as ciliary spasm from both pilocarpine 2% and Ocusert

The equivalent effectiveness of Ocusert and pilocarpine in glaucoma simplex cases has been shown in many reports (Armaly 1973 Heilmann & Sinz 1974 1975 Heilmann 1975 1977 Hennig 1976 Leydhecker et al 1975) In this investigation a similar result was also obtained in 5 glaucoma congestivum chronicum and 12 glaucoma capsulare cases in addition to the glaucoma simplex patients

Heilmann (1975b) reported in his 15-month investigation that in 41% of the patients (total 17) Ocusert remained in place throughout the entire study The

Table I
The causes of the failure and difficulties of using Ocusert® unit over one week

Difficulties and failures with Ocusert	Number of eyes tested
Fallen out*	19
Fallen out and replaced	2
Displaced	3
Distorted	7
Insufficient effectiveness	8
Patient s reluctance	9
All eyes tested	59
Difficulties and failures all together	
	41/59
* Absolute disadvantage	19 52 eyes = 3?%
Relative disadvantage	22 59 eyes = 4?%

result of Hennig s (1976) material of 53 patients tested under five weeks st[illegible] Ocusert remained in place in 64% of the patients In this study in 3?% of the e examined with Ocusert the result was good and compatible (Table I)

In Hennig s group 28% of the patients complained of irritation in the eyes this investigation these symptoms appeared in 4 of the cases but disappeared afte or 4 days

Heilmann (1975a) and Lienert & Busse (1975) noticed that Ocusert could tw around its longitudinal axis in a figure-of-eight This lessened its effectiveness a caused irritation in some patients In this study this was observed in 7 cases b seemed to be with minimal subjective symptoms and without perceptable effect the diurnal curve

Lienert & Busse (1975) and Leydhecker et al (1975) noticed that Ocusert in t upper cul-de sac caused less foreign body sensation than when placed in the low cul de sac This was also apparent in this study In the patient who had too shallow lower cul-de sac the upper one was sufficiently deep In some patients Ocusert observed to move spontaneously from one cul-de sac to the other Therefore wh Ocusert reached the inner canthus it fell out more easily than when moving past outer canthus With the exception of the first two cases all the Ocuserts were put under the upper eyelid

The greatest problem in the use of Ocusert® ocular delivery system seems to be weak permanence in the conjunctival cul-de sac without any present preventional possibilities The reduction of the tarsal tissue elasticity with age increases the ejection frequency we have noticed that patients over 70 years have a greater ejection frequency of Ocusert than younger patients The risk can be minimized if the patients are well instructed by the ward personnel in the use of the Ocusert® system

References

Armaly M F & Rao K R (1973) The effect of pilocarpine Ocusert with different release rates on ocular pressure *Invest Ophthal 12* 491–496

Heilmann K & Sinz U (1974) Ocusert ein neuartiges Medikamententragersystem fur die Glaukombehandlung 1 Mitteilung *Kl i Mbl Augenheilk 165* 519–524

Heilmann K & Sinz U (1975) Ocusert, ein neuartiges Medikamententragersystem fur die Glaukombehandlung 2 Mitteilung *Kli Mbl Augenheilk 166* 289–292

Heilmann K (1975a) Ocusert ein neuartiges Medikamententragersystem fur die Glaukombehandlung 3 Mitteilung *Klin Mbl Augenheilk. 167* 534–542

Heilmann K (1975b) Ocusert ein neuartiges Medikamententragersystem fur die Glaukombehandlung 4 Mitteilung *Klin Mbl Augenheilk 170* 109–119

Hennig J (1976) Pilocarpintropfen – Ocusert – Pilocarpin Eine vergleichende Untersuchung *Klin Mbl Augenheilk 169* 112–115

Lienert F & Busse H (1975) Ein Jahr Erfahrungen mit Pilocarpin Ocusert in der Glaukombehandlung *Klin Mbl Augenheilk. 167* 870 871

Leydhecker W Trapp S Linnert D & Gail M (1975) Ocusert Pilocarpin bei Glaukom simplex *Klin Mbl Augenheilk 166* 285–288

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TIMOLOL-MAINTENANCE TREATMENT

BY

B M CALISSENDORFF and N MAREN

Thirty-eight patients with ocular hypertension or glaucoma were treated with topical timolol for 12 30 months (mean 20) A long lasting hypotensive effect of timolol eyedrops was found However a need to increase therapy during the follow up period was noted especially in the glaucoma group Eyes with pseudoexfoliations often required concomitant therapy from the beginning Ocular side effects were relatively few but four cases of punctate keratitis and another two with decreased corneal sensitivity were observed

Key words timolol – follow up study – intraocular pressure – glaucoma – ocular hypertension – pseudoexfoliation – side-effects

Timolol maleate a beta adrenergic blocking agent reduces intraocular pressure (IOP) in normal (Katz et al 1976) and glaucomatous eyes (Zimmerman & Kaufman 1977 Krieglstein 1978)

The exact mechanism of action is not fully understood but the main hypotensive effect of timolol is attributed to a reduction of aqueous humour formation (Coakes & Brubacker 1978 Yablonski et al 1978 Sonntag et al 1979)

Timolol is a fairly new substance in the treatment of glaucoma Thus the question of long term drug efficiency and late side effects cannot yet be fully answered. Maintenance studies with an observation time of one to two years report good tolerance and good drug effectiveness of timolol (Boger 1978 Dausch 1978 Krieglstein 1979 Lin et al 1979 Nielsen & Eriksen 1979 Strempel 1979)

This study presents a long term follow up of timolol treated patients with open angle glaucoma or ocular hypertension

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Material and Methods

The study included 38 adults (20 males and 18 females) with an untreated intraocular pressure (IOP) > 22 mmHg in each eye Mean age was 66 years range 53 77 The patients were observed for 12 30 months (mean 20) Twenty five subjects were classified as chronic open angle glaucoma fulfilling one or more of the criteria glaucomatous vision field defect optic nerve cupping with a cup disc ratio (CDR) ≧ 8 or documented progress of CDR ≧ 2 The remaining 13 patients were considered as ocular hypertensions (OH) Exfoliative material was found in 13 eyes 10 in the glaucoma and 3 in the OH group

The study is a follow up of patients who previously had participated in a comparative study timolol/pilocarpine (Calissendorff et al 1980) The admission criteria as well as initial therapy regime is thus based on the protocol from that study

Timolol treatment was started with 0 25% solution once a day and in cases of unsufficient response (IOP > 22 mmHg) increased to 0 5% once or twice a day

Patients who in the comparative study received pilocarpine were switched to timolol in adequate concentrations

In the long term study pilocarpine was first choice for additional therapy Patients who in the comparative study received additional acetazolamide were switched to topical treatment if possible Only if combined topical therapy did not adequately reduce IOP was acetazolamide added

Repeated measurements of IOP > 22mmHg initiated changes in therapy In some cases an IOP slightly above the stipulated 22 mmHg was accepted if other factors pointed strongly against additional therapy and there was no sign of ocular damage

The patients were examined at least every three months Beside ocular examinations (including vision acuity cotton wisp testing of corneal sensitivity slit lamp observation Goldmann s applanation tonometry funduscopy and visual field test in Goldmann s perimeter) blood pressure and heart rate were registered Furthermore after one year s treatment with topical timolol diurnal pressure readings were performed

In those patients receiving acetazolamide the eye with the highest IOP determined the therapy In some cases topical therapy differed between the eyes and in cases where one eye needed the higher concentration of timolol for the convenience of the patient both eyes have been treated with the same solution Consequently the presentation of IOP values and therapy changes is based on the eyes with the highest IOPs In the report of side effects and of cases with exfoliations all eyes are included

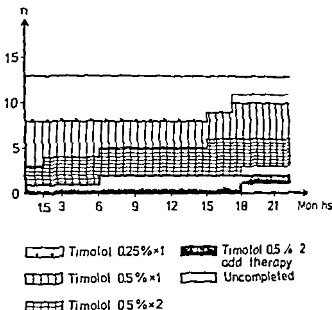


Fig 1

Distribution of therapy in 13 patients with OH during 21 months observation. Therapy changes induced by rise in IOP s

Results

The long term effectiveness of timolol maleate was studied for 12 30 months in 3 patients with elevated IOP During the follow up one patient age 76 years died from acute myocardial infarction and 5 dropped out for reasons reported below

Initially 20 patients could be controlled on topical timolol once a day and another 10 could be controlled with administration twice a day The number of patients with regulated IOP on topical timolol alone corresponds to 92% of the OHs and % of the glaucomatous eyes Eight patients in the study had concomitant therapy from the beginning

Figs 1 and 2 show the distribution of patients according to treatment and observation time for OHs and glaucomas respectively The presentations are restricted to the first 21 months of observation since thereafter the number of examined subjects markedly decreases Mean washout IOP was 29.8 (SD ± 4) mmHg for the OH and 32.6 (SD ± 6) for the glaucoma group According to Students *t* test there is no significant difference between those values ($P > 0.1$) After 12 months 24 patients remained on topical therapy corresponding to 92% 4

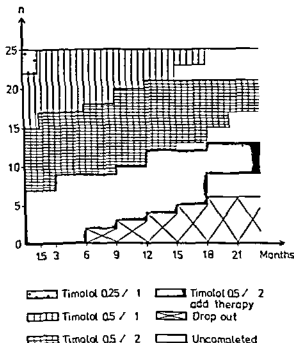


Fig 2
istribution of therapy and dropouts during 21 months observation of 25 patients with glaucoma Therapy changes induced by rise in IOP

e OHs and 52% of the glaucomas Thus the main part of subjects needing dditional therapy were glaucomas Compared to the OH group where the therapy mained rather constant the glaucoma group showed a shift towards higher oncentration of topical therapy as well as further additional concomitant therapy

Fig 3 shows the corresponding values for 13 eyes (10 glaucomas 3 OH s) with xfoliative lens material Seven of those eyes (54%) needed additional therapy from e start and after twelve months observation only 3 (23%) remained on topical erapy

Fig 4 presents mean IOP in 8 patients treated with timolol alone in unchanged oncentration during at least 21 months observation The material consisted of 3 atients with glaucoma and 5 with OH one in each group had pseudoexfoliations A significant reduction of mean IOP compared to pre-treatment level is seen hroughout the observation time and the pressure decrease is not significantly less t the end compared to the beginning of the study (paired t test)

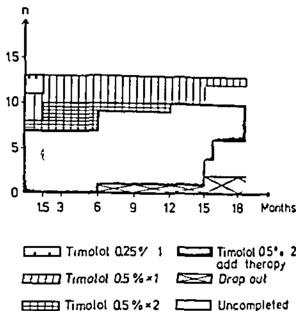


Fig 3
Distribution and changes of therapy in 13 eyes with raised raised IOP and exfoliation material observed during 18 months

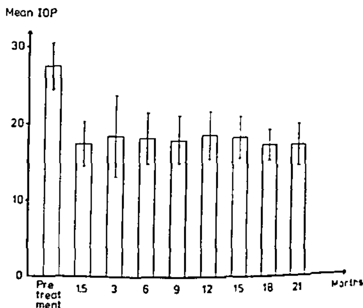


Fig 4
Mean IOP in 8 patients treated with timolol alone in unchanged concentration during months

T lle I
Ocular s gns bserved during stud

Decrea ed v sual cu v		4
V sual fel l defects d sco ered		e
V sual feld defects progress of		1 e
Punctate kera t s		1
Corneal anaesthes a		
Ir s		
H posphagma		e e
Conjunct t s		n
Burn ng ch ng drv e es at ns lla n		

Table I shows ocular s gns and svmtoms registered during he f llow up period me of the f nd ngs are probably not related to t nolol treatmen

A reduction of visual acuity was observed n 4 pat ents Sen le macular changes noted pre treatment were considered to expla n tl e reduct on n 1 case and a sl ght progress of cataract was observed in 3 patients T pat ents earl er treated with p locarp ne noted increased dependence on the r read ng glasses

During the observation t me a suspected progress n v sual feld defect was found n one e e and ne v defects were noted in 3 eves One of these ne v defects v as observed in a patient hose IOP at all regular observat ons had been well below 21 mmHg In sp te of max mum therapy 2 pat ents de eloped uncontrolled IOP and underwent surgery One pat ent n t ally c ntrolled with timolol needed add t onal therapy and was gi en p locarp ne As her IOP was controlled with p locarp ne alone the timolol medicat on as d scont nued

A sl ght burn ng sensat on when stilling the timolol drops and somet mes a l ght feel ng of dry eyes was reported by 6 pat ents Four pat ents stated a more p onounced fore gn body sensation and were found to ha e a superf cial punctate kerat t s Three of the kerat t s cases healed promptly when treated w th o ntment and cont nued all the t me with the r t molol med cation One of the keratitis cases wh ch started after a traumatic eros on needed fi e weeks before all signs and s mtoms were el minated During this time timolol eyedrops were excluded Later treatment was re admin stered and the patient has been observed for 11 months w thout any s gns f d scomfort or recurrance Corneal sens ti ty was normal n hese keratitis cases Reduced corneal sens t ity was fou d in 2 pat ents without any o her s mtoms After d scont nu ng the t molol n ed cat on the sens t vity impro ed w th n a few da s E ght pat ents had unspecif c conjuncti tis wh ch healed

spontaneously One patient had iritis which healed after two weeks treatment with topical atropine and cortisone Afterwards IOP remained controlled without timolol treatment and it was discovered that this patient had been receiving oral metoprolol for a fortnight He was therefore excluded from the study

No significant changes in blood pressure were observed during the follow-up period In the comparative study a low but significant reduction in pulse rate was observed However after a long period of timolol therapy pulse was no longer significantly low compared to baseline values (mean pulse rate before treatment 71 3 and after one year 70 5 beats/min) In one of the patients a congenital heart block caused a very slow pulse rate after 6 months observation Timolol was excluded The consulted internist considered that no cardiac therapy was necessary but timolol medication was stopped as a precaution One year later pulse rate still remained low

Discussion

This study affirms the impression of earlier maintenance studies that timolol has a long lasting hypotensive effect (Boger et al 1978 Dausch et al 1979 Krieglstein 1979 Lin et al 1979 Nielsen & Eriksen 1979 Strempel 1979) However in many cases in our study a gradual rise in IOP led to an increase in therapy This development is most pronounced in the glaucoma group where after 12 months observation only 32% remained on their initial therapy compared to 61% in the OH group Is this a sign of drug tolerance as recorded by Leydecker (1979) and Krieglstein (1978) or a progress in the severity of the glaucoma No definite answer can be given The more pronounced increase in therapy in the glaucoma compared to the OH group indicates an aggravation of the illness The findings in two of our glaucoma patients may also speak against drug tolerance although here a rebound effect as recorded by Krieglstein (1979) cannot be ruled out One patient without any previous therapy had after 11 months on topical timolol IOPs almost at pre treatment level Discontinuation of timolol resulted in a pressure rise clearly above previous pre treatment level Re administration of 0 5% timolol once a day gave a percentage pressure decrease quite comparable to the initial one The other patient had a capsular glaucoma and was controlled with pilocarpine before she entered the study Initially her IOPs were regulated with merely timolol but as time went on the IOPs increased Switching the therapy once again to pilocarpine didn't sufficiently reduce mean IOP but after additional timolol adequately controlled IOP was achieved

Raised IOP in eyes with pseudoexfoliations is more therapy re s ct t herts & anen 1978 Airaksinen 1979) a finding also reflected in this stu i I re retically reduced aqueous secretion could impair the outflow capa its wh h might ...ually endanger a capsular glaucoma. Hitherto repo rted tu es have not ...firmed the theory of reduced outflow in long term trea men w th imo ol Boyer et al. 1978 Dausch 1979 Lin et al 1979) and pecial reg r l was taken to capsular glaucomas in a six month follow up observation by A rak en (1979) A reduced aqueous formation might also interfere with normal len physiology No ...tain conclusion can be drawn from our 3 cases of cataract a he disorder is ...mmon in this age group All 3 patients had cataract bef e t molol was introduced and we have not been able to show any accelera io n of the process during the treatment

The ocular side effects in the present study include two cases of corneal ...aesthesia without any subjective symtoms and 4 cases of puncta e keratitis with ...rmal corneal sensivity van Buskirk reported (1979) corneal anaesthesia from ... maleate therapy In his cases as well as ours corneal sensitivity became ...al after discontinuation of timolol which indicates a local anaesthetic effect not a nerve damage Many β-blockers have membrane stabilizing activity i e ...l anaesthetic effect, a property which timolol is said to lack (Merck, Sharp & Dohme 1974) However it seems that chronic use of timolol can in susceptible ...dividuals cause corneal anaesthesia

Superficial punctate keratitis in timolol treated patients have been reported by ...c Mahon et al. (1979) and Nielsen & Eriksen (1979) None of the four keratitis in ...s study had corneal anaesthesia and all have continued with timolol therapy for ...veral months without recurrences A significant connection between timolol ...tment and keratitis is not proved Hypothetically the corneal epithelium could ... influenced by a mechanism similar to that found in rabbits where lacrimal ...oduction was reduced by β-blocking agents (Åberg et al 1979)

Timolol has been shown in the studies cited above as well as in our study to be a ...od hypotensive drug with rather few side effects However timolol treated ...ients should be kept under close observation in order to note any side effect At ...esent, corneal problems seem to be the major concern if timolol in the long run is ...fulfill its promise as a good alternative in the conservative treatment of glaucoma.

References

...ksinen P J (1979) The long-term h potensi e effect of timolol maleate compared with ...e effect of pilocarpine in simple and capsular glauc ma. Acta ophthal. (Kbh.) 57 425–434

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330 TRABECULECTOMIES
A LONG TIME STUDY (3–5½ YEARS)

BY

TORD JERNDAL and MATS LUNDSTRÖM

281 eyes out of 330 were followed during 3 to 5½ years after trabeculectomy. 39 eyes were drop-outs due to death and 17 eyes due to inability to participate in the examination program. The mean age at time of surgery was 66 years. A mean pre-operative IOP of 31 mmHg dropped to a mean post-operative level of 18 mmHg. In 57% a single trabeculectomy was considered enough to control the glaucoma. Post-operative medical treatment was considered necessary in 35%. In 87% the pre-operative progress of the field defect was arrested. A reoperation was performed in 8%. The early complications were very few, but in 25% a slowly developing cataract was observed. A cataract extraction was performed in 29 eyes post trabeculectomiam with a favourable visual outcome. This study confirms the opinion that trabeculectomy is an atraumatic and efficient surgical procedure and a necessary therapeutic measure when the tolerable combination of antiglaucoma drugs proves insufficient to control the glaucoma.

Key words: glaucoma – glaucoma surgery – goniodysgenesis – microsurgery – trabeculectomy

In 1977 we published a first study of 330 trabeculectomies followed for ½ – 3 years (Jerndal & Lundstrom 1977). Since the long term results after trabeculectomy are not sufficiently documented we decided to re-examine the material 3–5½ years after the operation. With a material of that scope it is our opinion that exhaustive documentation of the potentials of this surgical method may be possible.

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Technique

Most cases were operated under local anaesthesia Limbus based conjunctival and scleral flaps were performed

A trabeculectomy specimen was excised including the line of Schwalbe anteriorly and the scleral spur posteriorly

A basal iridectomy was made corresponding to the width of the trabeculectomy *For further details see Jerndal & Lundstrom (1977)*

Material

In Table I the number and sex distribution of the original material (330 eyes) and the present one (281 eyes) are specified 32 eyes were drop-outs due to death and 17 eyes due to inability to participate in the examination program or [illegible] to another area

Table II specifies the glaucoma classification of the operated eyes The classification is based on meticulous gonioscopy and sometimes modified by the [illegible] ings during surgery

We have also closely followed the criteria for glaucoma classification recommended by the International Symposium on Glaucoma in 1954 and cited by Duke-Elder (1969) The term late congenital glaucoma is defined glaucoma that is characterized by congenital goniodysgenesis and appears after infancy (Klusskens 1950 François 1953)

The high figure for late congenital glaucoma reflects the frequent occurrence of goniodysgenesis due to the detailed gonioscopic technique

All patients in the material had progressive field defects before operation and an IOP higher than 21 mmHg except those diagnosed as low tension glaucoma. No cases of ocular hypertension without visual field defects were included

Table I
Sex distribution

	Males	Females	Total
Number of operated eyes Original study 1977	146	184	330
Number of operated eyes Present [illegible] study	1_0	161	[illegible]
Drop-out	0	23	49

Table II

Distribution of specified glaucoma diagnosis (n = 281)

Late congenital glaucoma	157
Exfoliation glaucoma	101
Simple glaucoma	13
Pigmentary glaucoma	4
Closed angle glaucoma	5
Secondary glaucoma (uveitic)	1
	281

Table III

Mean post-operative reduction of IOP after trabeculectomy (281 eyes). The post-operative IOP was taken as the mean of the latest two values at ambulatory controls

Mean IOP by applanation	Period of observation (years)			
	3	4	5	5½
Pre-operative IOP	30	32	31	31
Post-operative IOP	16	16	18	19
Number of eyes	62	95	102	22

Table IV

Number of eyes with post operative IOP ≤ 21 mmHg after the therapy indicated (*n* = 244)

Therapy	Period of observation (years)			
	3	4	5	5½
Single trabeculectomy	37	62	53	9
Trabeculectomy combined with medical treatment	15	20	26	7
Re-operation (trabeculectomy)	3	2	0	2
Re-operation combined with medical treatment	0	2	5	1
	55	86	84	19

Results

All tonometry was performed with the Haag Streit applanation tonometer and the patient in a sitting position. The pre- and post-operative IOPs are plotted in Table III. A mean pre-operative IOP between 30 and 32 mmHg in the different follow up groups has dropped to a mean post-operative level of 16-17 mmHg. A slight tendency to a higher figure in the groups followed for 5 years and more is noted.

The figure for the pre-operative IOP was the reading on medical therapy when surgery was decided.

The figure for the post-operative IOP is the mean of the latest two values at ambulatory controls.

In Table IV the eyes with a post-operative IOP ≤ 21 mmHg are divided into four groups to demonstrate the post-operative additional therapeutic measures used.

It is seen that 161 eyes (57.3%, n = 281) were kept at an IOP ≤ 21 mmHg with a single trabeculectomy. With the various additional measures listed 244 eyes (86.8%, n = 281) were controlled at or below 21 mmHg.

The remaining 37 eyes are plotted in Table V. Thirteen of these have only had a single trabeculectomy and no post-operative treatment so far but are candidates for further antiglaucomatous therapy and thus have a very good prognosis for pressure control.

Table V
Number of eyes with post-operative IOP > 21 mmHg after the therapy indicated (n = 37)

Therapy	Period of observation (years)			
	3	4	5	5½
Single trabeculectomy		2	4	2
Trabeculectomy combined with medical treatment	1	6	8	0
Re-operation (trabeculectomy)	1	0	0	0
Re-operation combined with medical treatment	0	1	6	1
	[illegible]	[illegible]	18	3

Table VI
Number of eyes given post-operative medical treatment. Notice that the figures in the first two columns (1 and 2 years of observation) are taken from the previous study

	Period of observation (years)					
	1	2	3	4	5	5½
Number of eyes with post-operative medical treatment	15 (17%)	14 (29%)	16 (26%)	29 (30%)	45 (44%)	9 (41%)
Number of eyes in each group	86	46	62	95	102	22

A demonstration of the increasing need for post-operative medical treatment is seen in Table VI.

Table VII shows the post-operative development of the visual acuity. The most common cause of impaired visual acuity was a slowly advancing cataract.

In Table VIII we have attempted to list those eyes which displayed post-operative progressive *field loss attributable to glaucoma. Naturally in the presence of an* advancing cataract this was in some cases an almost impossible distinction.

Table VII
Post-operative change of visual acuity (n = 281)

Change of visual acuity	Period of observation (years)			
	3	4	5	5½
> +0.4		3	5	
+0.3 – +0.4	2	1	3	–
+0.1 – +0.2	4	9	8	–
±0	22	32	26	4
−0.1 – −0.2	11	20	19	7
−0.3 – −0.4	15	19	22	3
−0.5 – −0.6	5	5	10	2
−0.7 – −0.8	3	3	5	3
> −0.8		3	4	3
	62	95	102	22

Table VIII

Number of eyes showing post-operative progressive field loss due to glaucoma (n = 281)

Post-operative loss of field due to glaucoma	Period of observation (years)			
	3 (n = 6[illegible])	4 (n = 9[illegible])	5 (n = 10[illegible])	>5 (n = [illegible])
Number of eyes with IOP ≤ 21 mmHg	3	6	8	3
Number of eyes with IOP > 21 mmHg	1	6	9	1
Number of eyes irrespective of IOP (Percentage of each group)	4(6%)	12(14%)	17(1[illegible]%)	4(1[illegible]%)

The early post-operative complications were described in our first study (Jerndal & Lundström 1977). The only late complication in the present study was the development of cataract. In this study we have listed any lens opacities as a complication if they appeared or increased after the trabeculectomy and reduced the visual acuity two lines or more on the visual acuity test chart. According to this definition 70 eyes developed cataract in the post-operative observation period.

In 29 eyes therefore a cataract extraction was performed 1.5 years after the primary trabeculectomy. Various techniques for cataract extraction were used in order to avoid the filtering bleb e.g. extraction through an intracorneal incision or through an inferior corneoscleral incision.

The favourable visual results after these cataract extractions are shown in Table IX.

Table IX

Visual outcome in 29 eyes that were subjected to a cataract extraction after the initial trabeculectomy

Visual acuity	Before trabeculectomy	Before cataract extraction	After cataract extraction
0.[illegible] – 1.0	8	0	16
0.1 – 0.4	12		4
CF 1 – 4 m	5	11	3
< CF	4	8	[illegible]

Discussion

The introduction of a new surgical method for glaucoma will with necessity encounter a number of objections logical and historical as well as a great amount of scepticism The scientific approach to meet the objections and cleanse the air is to present the surgical results of trabeculectomy as detailed as possible This was attemted in our previous paper 330 trabeculectomies (Jerndal & Lundstrom 1977)

Not only are the details important but also the duration of the post-operative follow up Thirdly a sufficient number of cases is necessary in order to establish valid conclusions

With the present study on 281 eyes encompassing 3 5⅚ years after the original trabeculectomy we feel that valid conclusions are possible On the other hand it is not meaningful to prolong the follow up of the unselected material further because of the rapidly increasing drop-out frequency Already at this stage 49 cases have been lost because of death advanced senility or migration

The overall post-operative IOP is below 21 mmHg in all groups A comparison between the 1977 results and the present ones reveals that there is a slight trend for the long term groups to increase in tension It must be pointed out however that other therapeutic measures than the trabeculectomy were added according to Table IV It is evident that depending on the etiology and severity of the individual glaucoma a considerable variation of the therapy will be needed

Table IV demonstrates the post-operative additional therapy resulting in an IOP ≤ 21 mmHg For those eyes not controlled (IOP > 21 mmHg) the therapeutic measures are listed in table V As can be seen in the latter table 13 eyes out of 37 have so far only had a trabeculectomy and have not yet been put on additional therapy Most of these eyes have just passed the border of 21 mmHg in IOP and are in no way lost or have a particularly bad prognosis since the therapeutic possibilities are not exhausted

Eight eyes on the other hand have had the primary trabeculectomy reoperation and post-operative medical therapy without achieving control of the IOP ≤ 21 mmHg For these eyes the prognosis seems unfavourable unless a new therapeutic breakthrough occurs β-blocking agents may prove themselves helpful in that category In the 1977 report we concluded that after 1½ years the need for post-operative medical treatment was stable and approximately 30% This stable situation also holds for the 4 year group but not for eyes followed for 5 years or more For these eyes post-operative medical treatment was required in about 40% It is important to point out that for most eyes with glaucoma the natural history implies a progressively decreasing outflow facility The same appears to be valid for operated cases of glaucoma but to a lesser extent Therefore a post-operative

addition of medical treatment will be necessary for a proportion of the cases in our material between 30 and 10% Similar figures have been reported by others (Loewenthal 1977 Wilson 1977 Prialnic & Savir 1979)

The visual results after trabeculectomy must be viewed against the background of 1) the decay of visual acuity in the elderly 2) the glaucomatous decay and 3) the decay of visual acuity induced or accelerated by pre-operative antiglaucomatous drugs It has been demonstrated (Axelsson 1969) that the irreversible cholinester se inhibitors commonly used as antiglaucoma drugs have definitely cataract [illegible] properties This side-effect is particulary unwelcome in glaucoma, since it not only dims the vision of the patient but also diminishes the possibilities of the ophthalmologist to examine the optic disc and the visual field

In an unselected material of 60 medically treated cases of chronic glaucoma subsequently operated (Swegmark personal communication 1978) the decay in visual acuity during the year prior to the trabeculectomy was almost equal to the post-operative decay one year after trabeculectomy At the time of surgery visual acuity was worse in 51% of the cases equal in 34 [illegible] and better in [illegible] compared with one year before surgery Considering this 12 month pre-operative drop in visual acuity our post-operative results are not alarming (Table VII)

The post-operative drop in visual acuity was in most cases due to the development of cataract in other cases due to retinal degenerations vascular accidents vitreous opacities or other factors

No report on glaucoma therapy is complete without an analysis of the development of the visual fields One difficulty however is to define what changes are due to glaucomatous damage and what changes are due to retinal degenerations vascular accidents cataract vitreous opacities old age and poor correction of the refractive state Therefore a careful evaluation of each patient s efforts must be made With this in mind Table VIII may be scrutinized The aim of the anti glaucoma therapy is to arrest the glaucomatous process as judged by perimetry Thus the therapeutic efforts in this material achieved this goal in [illegible] cases (87%)

The post-operative complications after trabeculectomy are few To the [illegible] the original study of 1977 no complications have been recorded apart from the cataracts

It is not known if the surgical intervention per se is a significant cataract [illegible] incitament unless a direct complication occurs (haemorrhage [illegible] chamber etc) Age and genetic pre-disposition as well as a pre-operative [illegible] induced lens damage are factors that certainly play important roles for the final outcome

It is most encouraging to find however that a cataract extraction post trabeculectomiam poses no more surgical problems than an ordinary cataract extraction

Table X

Comparison of tension results and post-operative therapy aft glaucoma surgery Only the 4 year group of the present study is n lu led

	Greve & Dake (1979)	Jerndal & Lundstrom
Number of eyes	42	95
Follow up period (years)	4	4
Mean pre-operative IOP (applanation mmHg)	33 0	32 0
Mean post-operative IOP (applanation mmHg)	17 3	16 0
Mean drop of IOP	15 7	16 0
Post-operative medical therapy	9 (21 4%)	29 (30 5%)
Number of eyes re-operated	4 (9 5%)	5 (5 3%)
Total post-operative therapy (medical + reoperation)	13 (30 9%)	34 (35 8%)

Table IX) The psychological problem however may be greater for the patient nay not be so interested in a second operation when the first one according to his pinion made him blind

Consequently we think that a low risk of cataract development is no contraindica ion to trabeculectomy

Comparison of results after different surgical methods is notoriously frustrating ecause of the multiple discrepancies present One recent study by Greve & Dake 1979) presenting the four years results after double flap Scheie is sufficently imilar in design to allow a comparison of certain parameters as given in Table X The double flap Scheie can be described as a thermal trabeculostomy covered with ne laminar scleral and one conjunctival flap and as such is very similar to our rabeculectomy technique

The results are also strikingly similar

With the present paper we conclude the follow up of this unselected trabeculecto- ny material The information from this material is not exhausted however for an ppraisal of the survivors after e g ten years may add another piece of important nformation Our overall experience is that trabeculectomy is an atraumatic and fficient surgical procedure and a necessary therapeutic measure at the therapeutic ross roads i e when the tolerable combination of antiglaucoma drugs proves nsufficient to control the glaucoma

References

Axelsson U (1969) Glaucoma miotic therapy and cataract. Acta ophthal. (Kbh.) 47 35 ...

Duke Elder S (1969) System of Ophthalmology Vol XI p 389 Kimpton London

Francois J (1953) Le glaucome juvenile existe-t il Ann. Ocul. 156 801–810

Greve E L & Dake I (1979) Four year follow up of a glaucoma operation Prospective study of the Double Flap Scheie Int Ophthal 1 139–145

Jerndal T & Lundstrom M (1977) 330 trabeculectomies – a follow up study through ½–3 years Acta ophthal (Kbh) 55 52–62

Kluyskens J (1950) Le glaucome congenital Bull Soc Belge Ophtal 1– 45

Loewenthal L M (1977) Trabeculectomy as treatment for glaucoma a preliminary report Ann Ophthal 9 1179–1186

Prialnic M & Savir H (1979) Transient ocular hypertension following trabeculectomy Brit J Ophthal. 63 233–235

Wilson P (1977) Trabeculectomy long term follow up Brit J Ophthal 61 535 538

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FILTRATION BLEBS IN CORNEOSCLERAL V SUTURED WITH DEXON 7-0 AND DEXO

BY

JØRGEN KLEENER

In a retrospective investigation the incidence of post-operative suber njunctı l filtration with bleb formation were studied in 112 eyes which had underge ne cataract surgery with a corneoscleral incision sutured with braided pe lyglyc lic acid sutures (Dexon®) In 61 consecutive cataract operations sutured with Dexon 8-0 there were filtration blebs in 24 (39,3%) eyes and in 51 consecutive cataract operations sutured with Dexon 7-0 there were filtration blebs in 11 (21 6%) eyes Although there is a difference between the two materials this is not statistically significant with the normal security level $P < 0.05$

Key words filtrationblebs – corneoscleral suturing – absorbable sutures – cataract surgery

Per 1 8 1979 Dexon 7-0 was replaced by Dexon 8-0 as the suture material in catar ıct surgery at the Eye Clinic, Frederiksberg Hospital, Copenhagen In December 1979 a suspicion of an increased rate of conjunctival filtering blebs arose and the department therefore returned to the use of Dexon 7-0 sutures.

To study the problem more accurately all patients cataract operated with a corneoscleral incision and sutured with Dexon sutures during 1979 were clinically re-examined.

Dexon is the trademark of Davis and Geck, American Cyanid Company Pearl River New York, 10965

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Material and Methods

58 eyes were operated in the period 1.1.1979 to 31.7.1979 using Dexon 7 sutures. 68 eyes were operated in the period 1.8.1979 to 31.12.1979 using Dexon 8-0 sutures. Due to death and major diseases it was only possible to reexamine 51 consecutive eyes sutured with Dexon 7-0 and 61 consecutive eyes sutured with Dexon 8-0. The examination consisted of an evaluation of the corneoscleral wound, an evaluation of possible subconjunctival filtration bleb and an applanation tonometry.

All cases with Dexon 8-0 and subconjunctival filtration bleb were photographed.

The examination of the Dexon 7-0 material was performed one year after cataract surgery. The examination of the Dexon 8-0 material was performed from 3 to 8 months after cataract surgery.

The microsurgical technique used was the same in all 112 eyes. Limbal based conjunctival flap. Corneoscleral incision. 2 preplaced sutures at 1.30 and 10.30. Opening of the anterior chamber at 12.00 and widening with corneal scissors to approximately 160°. Peripheral iridectomy. Intracapsular kryoextraction of the lens. Tying of the pre-placed sutures, all as 2-1-1 knots. Finally continuous suturing of the conjunctiva and Tenon's capsule.

All patients received standard topical medication post-operatively: Scopolamine 0.2% twice and ultralanum cum chloramphenicol 4 times daily, normally for 4 weeks (5 mg fluorcortino pivalas and 2 mg chloramphenicolum in ricinioleum ad 1 g).

Table I

Age	Number of patients				
	Dexon 7-0		Dexon 8-0		
	Male	Female	Male	Female	
51 – 60 years	–	–	1	1	13
61 – 70 years	3	3	5	4	[illegible]
71 – 80 years	10	16	9	1	[illegible]
81 – 90 years	6	13	6	14	
Total	19	32	21	10	11

Table II

Number of sutures	Number of patients			
	+ filtration bleb		filt r	
	Dexon 7 0	Dexon 8 0	Dex i	
4	1	1		
5	6	16		
6	4	6	1	
7				
8			1	1
9				1
unknown		1		

Results

Age and sex (Table I) There was no difference in age and sex examined groups The corneoscleral wound was closed with *Dexon sutures* from 4 to 9 interrupted sutures (Table II) In were used of which 2 were pre placed 23% had 6 sutures (significant correlation between the number of sutures an i pearence of the filtration bleb though the filtration bleb did n more sutures had been placed

Subconjuncti al filtration bleb (Table III) occurred in 24 out of the 61 i (39 4%) where Dexon 8 0 was used When Dexon 7 0 was used 11 f i i operated eyes (21 6%) showed a subconjunctival filtration bleb With tan security levels ($P < 0.05$) there is no significant difference between the

Table III

	Number of patients		
	+ filtration	filtration	Total
Dexon 8 0	24	37	61
Dexon 7 0	11	40	51
Total	35	77	112

Table IV

Pressure difference post-operative – pre-operative Dexon 8 0 and Dexon 7-0 united

	Numbers of patients	
	+ filtration bleb	– filtration bleb
≥ + 6 mmHg	0	7
+ 1 → + 5 mmHg	2	18
0 → – 4 mmHg	9	40
– 5 → – 9 mmHg	16	9
– 10 → – 14 mmHg	6	1
≥ – 15 mmHg	2	0
unknown	0	3

materials As a whole the frequency of subconjunctival filtration bleb was 31 3% (Dexon 7 0 and Dexon 8 0 included)

The intraocular pressure (Table IV) showed great variation The difference between the post-operative pressure and pre-operative pressure (Table IV) was on average –6 mmHg in those cases where filtration bleb was found spreading from + 1 mmHg to –19 mmHg In the cases with no filtration bleb the difference between post operative pressure and pre-operative pressure in average was less than –1 mmHg spreading from + 9 mmHg to –10 mmHg

The variation of the pressure was so great that even a pronounced post-operative pressure fall cannot be taken as certain evidence for wound leakage with fistulation It is necessary to look for it

Discussion

It is usually reported that human limbal wounds in cataract surgery are healed after 10 12 days and firmly closed after 4 weeks (Jaffe 1972 Flaxel & Swan 1969)

Five days after surgery a limbus based conjunctival flap including Tenons capsule is firmly sealed (Flaxel & Swan 1969) The so-called remodelling starts 8 weeks after surgery and is completed after 2 2½ years (Jaffe 1972 Flaxel & Swan 1969)

Dexon 7-0 as well as Dexon 8-0 and Vicryl 8-0 are recommended in cataract rgery even for outpatient cataract surgery (Williamson 1976, 1977).
Blades (1979), Furgiule (1974), Sherman (1979), White & Porks (1974) and illiamson (1974) report almost concurrent good results after the use of Dexon tures. No marked post-operative tendency for filtration blebs is reported.
Based on suspicion of increased rate of filtration blebs after a period of 6 months e of Dexon 8-0 sutures, this investigation took place.
Sugar (1975) reports 11 filtration blebs in 156 cataract operations utilizing Dexon 0 sutures and 4 in 70 cases utilizing Dexon 7-0. Klemetti (1979) reports filtration ebs in 17 of 108 cataract operations with use of Dexon 7-0 sutures (15.7%). In the esent study frequency of filtration blebs is 39.3% for Dexon 8-0 and 21.3% for exon 7-0. It is reported (Sugar 1975, Klemetti 1979) that some filtration blebs sappear spontaneously. Therefore it must be born in mind that in the present idy there is a difference between the Dexon 7-0 and the Dexon 8-0 material in the ngth of the period from cataract surgery to reexamination.
Katz & Turner (1970) have experimentally shown that the tensile strength of 4-0, 2-0, 0 and 1 size of Dexon sutures had decreased 50% at 11 days and about % at 15 days. Craig et al. (1975) reported that both 2-0 and 4-0 Dexon sutures nderwent a sharp decline in strength already seven days post-operative. Twenty days post-operatives there is no measurable breaking strength left. Blades 979) reports that Dexon 7-0 sutures disappeared after 43 days and Dexon 8-0 35 days.
Klemetti (1979) concludes: Dexon 7-0 sutures cannot be recommended in taract surgery in which the long term rentention of suture tensile strength is sential for wound healing. This report shows an even more marked tendency for ost-operative filtration blebs as those reported by Klemetti (1979). But why this eat discrepancy in the different reports about post-operative filtration blebs after exon sutures?
The filtration blebs are actually not seen or they appear after discharge of the atient from hospital. A plainly retrospective examination of the medical records ad not exposed the real number of conjunctival filtration blebs. Only reexamina on of the patients did.
Increased use of post-operative topical medication with steroid could delay the ound healing. Glucocorticoids are well known to have an inhibitory effect on the proliferation of mesenchymale cells and the production of intercellular macromole cules included collagen. With the knowledge from Craig et al. (1975) of the sharp deceline in tensile strength of Dexon sutures already after seven days, the explanation of a high rate of filtration blebs post-operatively could be the post-operative use of steroids. Sugar (1975) reports use of 0.1% dexamethasone from the 5th day until 5 weeks after surgery. Klemetti (1979) used 0.1% dexa

methasone 4 times daily from the first day to the 8th day after surgery The patients in this report received droplets containing 5 mg fluocortinol pivalas and 2 mg chloramphenicolium in ricini oleum ad 1 g from the first post-operative day

Although no exact conclusion can be drawn it seems justified to avoid use of heavy steroids especially in the first weeks after sugery if Dexon sutures are preferred in cataract surgery

References

Blades I E (1976) An evaluation of 8-0 polyglactin 910 absorbable suture in cataract surgery *Ophthal Surg 7* 55–61

Blades I E (1976) An evaluation of 8-0 polyglycalic acid braided synthetic absorbable suture in cataract surgery *Ann Ophthal 11* 963–965

Craig I H Williams J A Davis K W Magoun A D Levy A J Bogdansky S & Jones J P (1975) A biologic comparison of polyglactin 910 and polyglycolic acid synthetic absorbable sutures *Surg Gynec Obstet 141* 1–10

Flaxel J T & Swan K C (1969) Limbal wound healing after cataract extraction *Arch Ophthal (Chicago) 81* 653–659

Furgiuelle F I (1974) Ophthalmic use of a new synthetic suture (Dexon) *Ann Ophthal 6* 1219–1225

Jaffe N S (1972) Cataract Surgery and its Complications p 90 and p 161 C V Mosby Saint Louis

Katz A R & Turner R J (1970) Evaluation of tensile and absorption properties of polyglycolic acid sutures *Surg Gynec Obstet 131* 701–716

Klemetti A (1979) Rate complications of 7 0 polyglycolic (Dexon) sutures in cataract surgery *Acta ophthal (Kbh) 57* 33–40

White R H & Parks M M (1974) Polyglycolic acid sutures in ophthalmic surgery *Trans Amer Acad Ophthal 78* 632–636

Williamsson D E (1976) The use of polyglycolic acid sutures in outpatient cataract surgery *Ann Ophthal 8* 333–340

Williamsson D E (1976) The use of 8-0 Dexon and 8 0 Vicryl in outpatient cataract (IOL implant surgery *Contact & Intraocular Lens Med J 3* 47–48

Sherman S E (1979) Evaluation of an improved suture for cataract surgery *Ann Ophthal 11* 269–271

Sugar H S (1975) Further use of polyglycolic acid (Dexon) sutures in intraocular surgery *Ann Ophthal 7* 125–129

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ON THE FORMATION OF ELSCHNIG S PEARLS A TISSUE CULTURE STUDY OF REGENERATING RAT LENS EPITHELIUM

BY

PER P FAGERHOLM

Rat lens epithelial cells were allowed to regenerate on the lens capsule in tissue culture The major part of the lens fibers had been removed After a month spherical bodies appeared similar in appearance to Elschnig s pearls Electron microscopical examination revealed that these spheres consisted of large extracellular vacuoles and phase contrast examination revealed a cont nuous change in appearance of these spheres The mechanism behind the tendency to form extracellular vacuoles probably include an increased extrusion of sodium and water from osmotically stressed lens cells

Key words rat lens epithelium – after-cataract – Elschn g s pearls – tissue culture – phase contrast microscopy – electron microscopy

Elschnig s pearls a specific form of after cataract are sometimes seen on the posterior capsule after lens trauma or extracapsular cataract extraction (Hirschberg 1901 Elschnig 1911) These transparent spheres appear singly or in aggregates varying in individual size up to two mm in diameter The individual spheres may form and vanish continuously The tendency to form Elschnig s pearls may be followed in the slit lamp microscope over several years and they may cause severe reduction in visual acuity (Cowan & Fry 1937) Of the several ways of treatment suggested the surgical approach is now preferred (Gundersen 1966) Histologically the Elschnig s pearl has been described as one giant cell formed by a regenerative attempt of the lens epithelial cells after lens trauma (Cowan & Fry 1937)

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simultaneous increase in tissue mass underneath the capsular folds was observed four of the specimens however little or no regenerative activity could be identifie In all these cases the other specimen in the same flask showed more extensi regenerative signs

After 4 8 weeks transparent spheres emerged from folds in 9 of the preparations (Fig 2 A and B) Generally there was a continuous change in size a number of these spheres In three of the specimens a continuous overall increase size and number of the spheres was noted during the following 4 8 weeks

Histological and TEM examination

The main cellular regeneration was identified underneath the extremely fold capsule (Fig 3) However in som of the specimens cellular growth outside t capsular folds was extensive (Figs 4 and 5B) The latter cells were as a rule more l lens fibers in that they were elongated and had very few cell organelles Howev they generally retained their nuclei Large or swollen cells were sometim

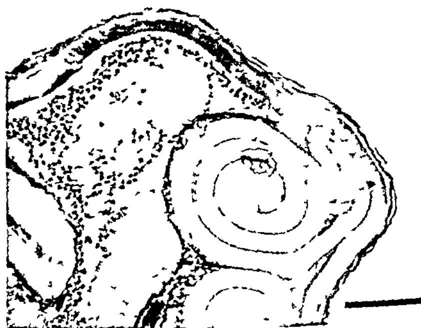


Fig 3
Epithelial cell regeneration underneath a thickened and wrinkled capsule Most cells retai their epithelial appearance and no tendency towards extracellular vacuole formation co be seen Toluidine blue Bar 100 μm



Fig 4

:generation of lens cells mainly outside the capsule disclosed lensfiberlike cells with abundant extracellular acuoles of different sizes Toluidine blue Bar 100 µm

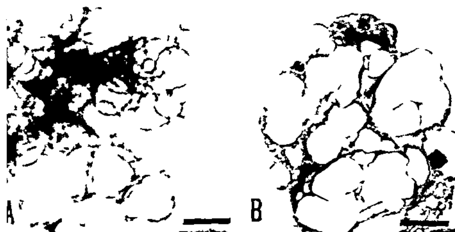


Fig 5

A Phase contrast micrograph of transparent spheres at the surface of a capsule preparation after 10 weeks in tissue culture B Histological section through the transparent spheres re ealed large extracellula acuoles Toluidine blue Bar 100 µm

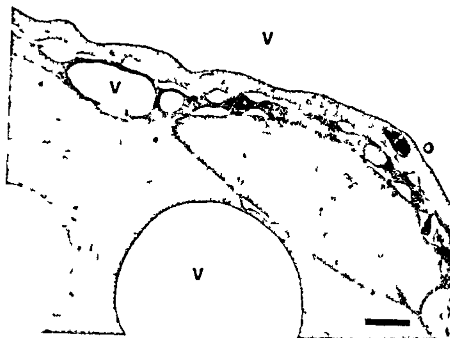


Fig 6
Electron micrograph from the same specimen as in Fig 5 Very few cell organelles are seen i the sometimes extremely flattened cells Extracellular vacuoles (v) of different sizes wer abundant Bar 1 µm

identified In the specimen with this latter type of cellular regeneration extracellula vacuoles were abundant The size of these vacuoles could be measured up to 0 1 mm in diameter (Fig 5A) The lensfiber like cells in between these very large vacuoles were extremely thin down to 0 3 µm (Fig 6)

Discussion

In the slit lamp microscope and on histological examination Elschnig s pearls have been regarded as giant cells (Cowan & Fry 1937) The technical problems inherent in the method of surgical removal (Gundersen 1966) probably disrupt these delicate structures and thus explain the scarcity of morphological studies

The regeneration of human and rabbit lens epithelium in tissue culture has previously been demonstrated using flat mount preparations (Fagerholm & Philip-

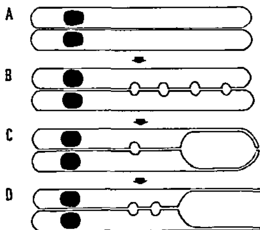


Fig 7

Schematic drawing showing a possible mechanism behind the formation of transparent spheres The lens fiber like cells (A) respond to osmotic stress influenced by the untoward ionic composition in the aqueous humor by forming extracellular vacuoles (B) These vacuoles coalesce to form giant vacuoles (C) that eventually rupture (D) and the process is then restarted

son 1977) The present study was focused on the structures that in the phase contrast microscope are very similar to Elschnig's pearls These structures were not observed in the flat mount preparations of human and rabbit lens capsule probably due to the shorter observation period less than of six weeks (Fagerholm & Philipson 1977) The tissue culture procedure with a free floating capsule allowed atraumatic preparation for the electron microscopical examination

The transparent spheres were shown to be extracellular vacuoles The vacuoles were surrounded by often very thin cells resembling lens fibers The change in appearance suggests a continuous formation of extracellular fluid by the lensfiber like cells The rat lens epithelium regenerated tending to differentiate to lens fibers The cells elongated and lost most cell organelles but retained their nuclei Normally the lens fiber differentiation takes place inside the lens capsule The ionic milieu here is compatible to the restricted capacity of mature lens fibers to resist ionic changes (Fagerholm 1979) However differentiation in the aqueous will probably reach a point where the lens cells have difficulty in withstanding the ionic load of the aqueous Lens fibers are probably reacting to osmotic stress by increasing the transport of sodium and thereby water into the extracellular space Extracellular vacuoles will then be formed (Sakuragawa et al 1975) This mechanism (Fig 7) and the appearance and dynamics of the spheres are very similar to the behaviour and appearance of Elschnig's pearls (Cowan & Fry 1937)

Elschnig s pearls as seen in the slit lamp microscope may consist of several types of formations including giant extracellular vacuoles Morgagnian spheres and perhaps enlarged lens fibers Several types of cellular response constitute the different forms of after cataract In the absence of inflammation the end result seems to be dependent on the degree of mitotic activity and the degree of cellular differentiation The latter probably determines such factors as production of new capsule material as well as the degree of extracapsular vacuole formation

Further studies are required of which factors determine cellular properties in order to find a non surgical treatment of after-cataract

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References

Cowan A & Fry W F (1937) Secondary cataract with particular reference to transparent globular bodies *Arch Ophthal (Chicago) 18* 12–22

Elschnig A (1911) Klinisch anatomischer Beitrag zur Kenntnis des Nachstares *Klin Monatsbl Augenheilk 49* 444–451

Fagerholm P P & Philipson B T (1977) Formation of aftercataract by regeneration of human and rabbit lens epithelium in tissue culture *Acta ophthal (Kbh) 55* 369–3?1

Fagerholm P P & Philipson B T (1979) Human traumatic cataract A quantitative microradiographic and electron microscopic study *Acta ophthal (Kbh) 57* 20–39

Fagerholm P P (1979) The influence of calcium on lens fibers *Exp Eye Res 28* 211–222

Gundersen T (1966) Surgical management of Elschnig s pearls *Amer J Ophthal 61* 1124–1127

Hirschberg J (1901) Einfuhrung in die Augenheilkunde Georg Thieme Leipzig p 129 quoted by Vogt A (1931) Lehrbuch und Atlas der Spaltlampen Mikroskopie des lebenden Auges p 634 Julius Springer Berlin

Sakuragawa M Kuwabara T Kinoshita J H & Fukui H N (1975) Swelling of the lens fibers *Exp Eye Res 21* 381–394

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CENTRAL CORNEAL THICKNESS AND INTRAOCULAR TENSION IN PATIENTS WITH ACROMEGALY

BY

THORKILD BRAMSEN, ANNE KLAUBER and PER BJERRE[1]

In 27 patients with pituitary adenomas the central corneal thickness and the intraocular tension were measured. Thirteen of the patients were suffering from acromegaly and in this group the central corneal thickness was 0.561 mm ± 0.035 ($\bar{x}$ ± SD). In the 14 patients with pituitary adenomas but no acromegaly the central corneal thickness was 0.526 mm ± 0.030 ($\bar{x}$ ± SD). This difference is statistically significant $0.01 > P > 0.001$.

In the 13 patients with acromegaly the intraocular tension measured by applanation was 16.9 mmHg ± 2.3 ($\bar{x}$ ± SD) and in the control group 14.7 mmHg ± 2.4 ($\bar{x}$ ± SD). This difference is statistically significant ($0.05 > P > 0.02$). When the applanation reading is corrected for the difference in the central corneal thickness, the patients suffering from acromegaly have an intraocular tension of 14.1 mmHg, which is of the same magnitude as the tension in the patients without acromegaly.

Key words: acromegaly – central corneal thickness – pituitary adenoma – intraocular tension.

In adults growth hormone producing pituitary adenomas often result in acromegaly characterized by growth of peripheral parts of the body, i.e. bones as well as soft tissues. Important to the general appearance is the thickening of the facial soft parts.

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Decrease of the acromegalic changes of the soft tissues is an important indicator of successful treatment. No methods exist for measuring this. Growth hormone analyses are of limited value, because the correlation between plasma growth hormone level and clinical activity of the disease is poor (Lindholm 1979). If the cornea takes part in the thickening of the soft tissues, measurement of the central corneal thickness (CCT), which can be performed with great accuracy, would possible be of importance in the diagnosis and the control of the acromegalic patient. Ehlers & Bramsen (1978) found in 45 conscripts a CCT of 0.510 mm ± 0.027 (mean ± SD).

Increased intraocular tension has been described with a high frequency in patients with acromegaly (Aren & Skanse 1955, Howard & English 1965). If the CCT increases with acromegaly, it would be assumed that the applanatory values will increase and thus falsely indicate increased intraocular tension (Ehlers et al. 1975).

The purpose of this investigation has been to measure the CCT and the intraocular tension in patients with pituitary adenomas with and without acromegaly.

Material and Methods

The material consists of 27 patients with pituitary adenomas verified by X-ray examination or operation. CCT was measured with a modified Haag Streit pachometer as described by Ehlers & Sperling 1977.

The coefficient of variation of the CCT measurement is for a trained examinator about 1% (Olsen et al. 1980). The intraocular tension was measured by applanation tonometer as described by Goldmann. Measurements were performed by the two ophthalmological authors and the mean value of the two eyes was used in the calculations. The examining ophthalmologists were unaware of the case records and the diagnosis. Obviously acromegaly could often be identified at a glance. The participating neurosurgeon was ignorant of the CCT until the conclusion of the study.

Included were 13 patients with acromegaly, seven females and six males. The average age was 46.7 years ranging from 23 to 68 years. The duration of the disease varied from 1.5 to 17 years.

In the group of pituitary adenomas without acromegaly were included 14 patients, eight females and six males. The average age was 43.1 years ranging from 23 to 63 years. The duration of the disease was from 0.5 to 17 years.

Table I

CCT applanation readings and corrigated applanation readings = intraocular tension in patients with pituitary adenoma with and without acromegaly

	Patients with pituitary adenoma	
	with acromegaly (N = 13)	without acromegaly (N = 14)
CCT mm ± SD	0 561 ± 0 035	0 526 ± 0 030
Applanation readings mmHg ± SD	16 9 ± 2 3	14 7 ± 2 4
Corrigated applanation readings Intraocular tension mmHg ± SD	14 1 ± 2 3	14 2 ± 2 4

Results

The result of the measurements of the CCT and the intraocular tension appear from Table I

The difference in the CCT between the two groups is significant $0\ 01 > P > 0\ 001$

The difference in the direct applanation readings between the two groups is significant $0\ 05 > P > 0\ 02$

No difference in corrigated applanation readings is found between the two groups

Discussion

The investigation has shown that in patients with acromegaly the CCT is increased compared to patients with pituitary adenomas without acromegaly suggesting a hypertrophic effect of growth hormone on the corneal tissue

The present investigation does not show which layers of the cornea are responsible for the increased CCT At slitlamp examination and during the pachometer measurements the cornea appeared normal especially without any signs of oedema Within both groups a considerable variation in the CCT was noted In the acromegaly group this might be explained by different levels of endocrine activity An investigation on this has been started In the control group there are two

patients who are suspected of having acromegaly and where only a period of observation can decide the final diagnosis

The investigation also demonstrated increased applanation values in patients with acromegaly compared to patients with pituitary adenomas without acromegaly

As mentioned in the introduction a connection has already been noticed between increased applanation readings and pituitary adenomas Especially during the 1960 s this led to discussions (Codtfredsen 1968) Naturally patients may occur with both glaucoma simplex and acromegaly as independent diseases The increased applanation readings in the acromegalic patients of this investigation are due to a misinterpretation of the measured tension values as it has already been shown (Ehlers et al 1975) that an increased CCT leads to higher applanatory values If the applanation readings in this group corrected for the increased CCT the acromegaly patients have a true intraocular tension of 16 9 mmHg – 2 8 mmHg = 14 1 mmHg which is of the same normal magnitude as in the group without acromegaly The corresponding figures for patients with pituitary adenomas but no acromegaly were 14 7 mmHg – 0 5 mmHg = 14 2 mmHg

References

Aren A & Skanse B (1955) On non inflammatory glaucoma in acromegaly *Acta ophthal (Kbh) 33* 295–306

Ehlers N Bramsen T & Sperling S (1975) Applanation tonometry and central corneal thickness *Acta ophthal (Kbh) 53* 34–43

Ehlers N & Sperling S (1977) A technical improvement of the Haag Streit pachometer *Acta ophthal (Kbh) 55* 333–336

Ehlers N & Bramsen T (1978) Central thickness in corneal disorders *Acta ophthal (Kbh) 56* 412–416

Codtfredsen E (1968) Glaucoma and pituitary tumour *Acta ophthal (Kbh.) 46* 600–604

Howard C M & English F P (1965) Occurence of glaucoma in acromegalics *Arch Ophthal (Chicago) 73* 765–768

Lindholm J (1979) Assessment of pituitary function *Acta Neurol Scand 59* 161–171

Olsen T Nielsen C B & Ehlers N (1980) On the optical measurements of corneal thickness *Acta ophthal (Kbh) 58* 760–766

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ON THE OPTICAL MEASUREMENT OF CORNEAL THICKNESS

II The Measuring Conditions and Sources of Error

BY

THOMAS OLSEN CARSTEN BO NIELSEN and NIELS EHLERS

The optical measurement of corneal thickness based on oblique viewing of the optical section of the cornea is complicated by the finite width of the incident slit beam In this report the theoretical and practical aspects of the effect of the slit width on the thickness reading are analysed In practice it was not possible to make slit width independent thickness readings which were reproducible from one observer to another In addition the observed slit width error was found to vary from one patient to another The lack of a reproducible estimate of the corneal thickness is attributed to difficulties associated with an exact definition of the edges of the visible bands of the optical section which are determined by biological properties of the cornea as well as perceptive properties of the observer

Although inter-observer errors up to 0 02 mm were found the intra-observer error amounted to only 0 005-0 006 mm (SD) between consecutive readings Presumably this high intra-observer reproducibility is the result of the auxiliary pin lights used Changes in corneal thickness measured by the same observer can therefore be determined with great accuracy

Key words corneal thickness – pachometer – reproducibility

*The optical measurement of corneal thickness (pachometry) is becoming increa*singly employed in ophthalmological practice One of the most widely used methods is based on the principle described by Jaeger (1952) involving oblique viewing of an optical section of the cornea produced by an incident slit light normal to the corneal surface One advantage of this method is that the theoretical

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performance and errors of the measuring system can be calculated in a straightforward manner (Olsen et al 1980) However despite the theoretical simplicity the normal" values reported by different investigators still differ considerably even with the same commercially available equipment It therefore seems that the measuring conditions need some considerations We report herein an analysis of some of the practical errors concerned with the optical measurement of corneal thickness

Methods

A Haag Streit 900 slit lamp with pachometer attachment was used throughout the experiments To secure perpendicular direction of the slit beam on the cornea a pin light attachment (Ehlers & Sperling 1977) was mounted on the pachometer attachment according the principle of Mishima & Hedbys (1968) The pin light attachment can be purchased from NOCO Copenhagen Denmark The luminance of the slit light was always kept at a maximum (using over voltage 7 5 V with lamp 6 V 4 5 A) We were not able to determine the exact luminance of the slit light However when the focused slit beam of 0 03 × 18 mm was entered into a lux meter (window 14 × 28 mm normally used for the Goldman perimeter) the reading was about 180 lux Room light was dim (less than 50 lux) The examinators (N E T O C B N) had normal visual acuity and were adapted to room light at least 10 min before the thickness readings were started They were all trained thickness examinators (several months to several years of daily experience) All series of thickness measurements were performed in a blind fashion That is the alignment of the two half images of the beamsplitter was done by the examinator while the scale of the pachometer was read by another observer without telling the examinator Each reading was taken as the closest 5 μm position on the scale reading of the pachometer The readings were used directly no corrections being made for corneal curvature or non linearity of the pachometer Between each reading the pachometer was put out of adjustment

The width of the focused slit light was measured by counting the number of 0 01 mm divisions of an object micrometer (Leitz) perpendicularly illuminated by the slit while the slit image was viewed through the pachometer eyepiece The reading was reproducible to 0 005 mm

For multiple comparisons of means analysis of variance was applied (Sokal & Rohlf 1969)

Results

Theoretical considerations

The optical section of the cornea made by the slit light is a three-dimensional structure The antero-posterior dimension is made by the cornea itself the width is made by the slit width When the corneal section is produced by very narrow and almost parallel beams of light and viewed at an angle of 40 (= angle used in the Haag Streit pachometer) it is usually composed of a broad anterior bright band a

somewhat opticalls empty central zone and a narrow posterior bright band The anterior band results from scattering of the light in the epithelial layer The width of the anterior band (seen obliquely) is therefore determined for its most part by the thickness of the epithelium and for a smaller part by the width of the slit light The small width of the posterior band makes it appear as determined solely by the slit width Because the optical principle of the pachometer assumes no slit width the correct alignment of the two half images formed by the beamsplitter of the pachometer is therefore presumably not an end to-end alignment of the optical section but rather a side to-side alignment of the (left) slit edge (Fig 1 alignment A and B respectively)

An assumption of the latter alignment is that the width of the posterior band corrresponds to the width of the focused slit light

Although the exact anatomical basis for the posterior band of the optical section is unknown it seems evident that alignment A in Fig 1 would result in an over

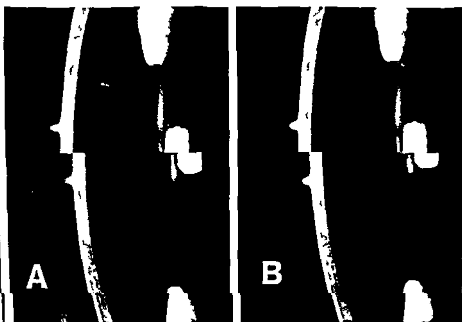


Fig 1

Optical section of the cornea viewed through the beamsplitter of the pachometer Two pin lights are reflected at the anterior limit of the section In A an end-to-end alignment of the optical section is shown If the narrow posterior band is assumed to represent the slit width a presumable slit width independent alignment is shown in B

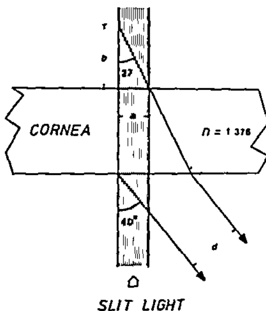


Fig. 2

When the optical section of the cornea is produced by a slit beam of measurable width (a) the slit width is thought by the pachometer to represent an additional thickness (b)

estimation of the corneal thickness. Assuming that the width of the posterior band corresponds to the width of the focused slit light, the expected magnitude of this overestimation can be calculated as follows (Fig. 2).

The angle of observation with the pachometer is 40°, but due to refraction at the corneal surface the slit width (a, Fig. 2) is seen at an angle which approximates 27° (from sin i/sin u = n assuming a plane cornea). Through the eye piece of the pachometer the slit width is seen as an additional part (b, Fig. 2) of the optical section, the thickness of which is the slit width multiplied by tg^{-1} (27°) = 1.9. (Again assuming no curvature of the cornea. If the corneal curvature is included in the considerations, the true angle at which the slit width is observed becomes smaller and the corresponding thickness of the slit width becomes greater.)

Although the Haag Streit model 900 slit lamp is provided with a scale reading for the slit width adjustment, it is not calibrated for a direct metric reading of the focused slit width. In Fig. 3 is shown the actual slit width (lower unbroken line) as a function of the scale reading on the slit lamp (valid for the slit lamp used for the present study. We have found this conversion function to vary slightly from one Haag Streit 900 slit lamp to another. Also the slit luminance was found to vary.) The lower part of the curve was seen to stabilize at about 30 µm corresponding to a reading of 8 or less, below which the slit was only faintly visible. Dotted line (closed

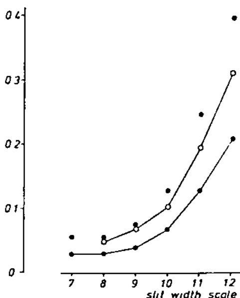


Fig 3

Closed circles unbroken line width in mm of focused slit light as a function of the arbitrary slit width scale on the Haag Streit slit lamp Closed circles broken line theoretical slit width error on the pachometer reading Open circles unbroken line observed slit width error calculated as the difference between the A and B readings shown in Fig 4

rcles) in Fig 3 indicates the expected error with alignment A (actual slit width × 9) on the corneal thickness estimation

hickness measurements

n order to test the validity of the above mentioned considerations the corneal ickness of a normal 27 year-old subject was measured with alignment A and B sing a number of different slit width settings (Fig 4) As expected the corneal ickness readings with alignment A were greatly influenced by increasing slit idth The readings with alignment B were however also slit width dependent but the opposite direction (one way analysis of variance showed $P < 0.001$) The ifference between the two readings i e the apparant slit width error has been cluded in Fig 3 (open circles) It is seen to be lower than the expected error

The visible width of the posterior bright band of the optical section did thus not orrespond to the directly measured width of the slit.

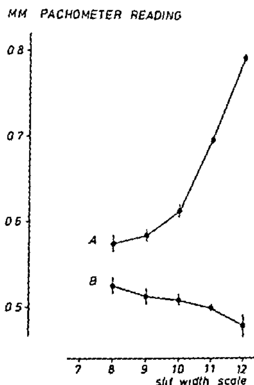


Fig 4
I achometer reading as a function of slit width using two methods of alignment A and B
Each point is the mean of six determinations Bar = sD

In order to study the reproducibility of the corneal thick
whether the apparent slit width in the posterior corneal
variability six corneas (from six patients with senile
years) were measured with the pachometer using alternat
= 6) The slit width was 30 µm The expected difference
is 57 µm (30 µm × 1 9) From Table I it is seen that this
any of the cases

Analysis of variance (Table II) showed the mean
differ among the three examinators for alignment
largest observed difference in means was 0 022
mm with alignment B Although the inter-observe
well as in alignment B thus was appreciable
(standard deviation) was only 0 0051 mm and 0 006

Table I

Mean value of central corneal thickness readings (n = 6) and their standard deviations (in parenthesis) obtained using two methods (A and B) of alignment The difference between the two readings is the apparent slit width error Actual slit width is 0 030 mm which theoretically *should induce an error of 0 057 mm (see Fig 2)*

Examinator	N E.			T O			C B N		
Alignment	A	B	A B	A	B	A B	A	B	A B
Patient No									
1	0 568	0 543	0 025	0 569	0 542	0 028	0 584	0 553	0 032
	(0 006)	(0 007)	(0 006)	(0 004)	(0 005)	(0 003)	(0 005)	(0 010)	(0 011)
2	0 509	0 477	0 033	0 513	0 468	0 045	0 531	0 481	0 050
	(0 005)	(0 005)	(0 004)	(0 004)	(0 005)	(0 006)	(0 004)	(0 012)	(0 012)
3	0 537	0 512	0 025	0 545	0 506	0 039	0 556	0 518	0 038
	(0 007)	(0 008)	(0 010)	(0 003)	(0 005)	(0 006)	(0 007)	(0 007)	(0 012)
4	0 548	0 516	0 032	0 538	0 508	0 031	0 543	0 507	0 036
	(0 005)	(0 005)	(0 008)	(0 003)	(0 004)	(0 004)	(0 006)	(0 006)	(0 003)
5	0 538	0 522	0 016	0 544	0 518	0 026	0 547	0 515	0 032
	(0 005)	(0 005)	(0 007)	(0 004)	(0 004)	(0 004)	(0 006)	(0 005)	(0 007)
6	0 563	0 536	0 028	0 574	0 555	0 019	0.583	0 551	0 033
	(0 006)	(0 006)	(0 004)	(0 004)	(0 005)	(0 009)	(0 005)	(0 006)	(0 005)

respectively The intra-observer A error was significantly ($P < 0\ 05$) less than the B error The intra-observer mean difference between reading A and B that is the apparent slit width error varied from 0 016 to 0 050 mm and was found to differ from one examinator to another but also from one patient to another In all three instances alignment A and B and their difference a significant interaction was found between the patient and the examinator

Table II

Two-way analysis of variance of data summarized in Table I

		F Value		
Source of variance	df	A	B	A B
Between rows (patients)	5	not tested	not tested	14 3
Between columns (examinators)	2	31 5 *	4 0	15 6
Interaction	10	5 5	5 2	2 9

$P < 0\ 05$ $P < 0\ 001$

Discussion

The intra-observer readings in the present study showed a high degree of reproducibility For example a standard deviation of 0 005 mm (about 1%) as found for alignment A (Fig 1) means that a given single reading was accurate to ± 0 010 mm (95% limit) Presumable this small intraobserver error is the result of the auxiliary pin lights used which secures a perpendicular corneal illumination and a fixed observation angle A similar small error was reported by Donaldson (1966) who was the first to apply auxiliary pin lights in order to increase the stability of the measuring situation

However an inter-observer reproducible estimate of the corneal thickness was not possible with the present methods of measurement The reason for this may be indicated in the slit width error analyses Based on edge alignments of the posterior band of the optical section the actual error produced by the posterior band on the thickness reading was found to be smaller than expected from direct measurements of the slit width This indicated that what is seen as the posterior band of the optical section is dependent on biological properties of the cornea in addition to physical properties of the slit light The biological nature of the apparent slit width was also illustrated by the different errors produced from one patient to another Furthermore the slit width error differed from one observer to another indicating that the recognition of the posterior band is subject to perceptive variability

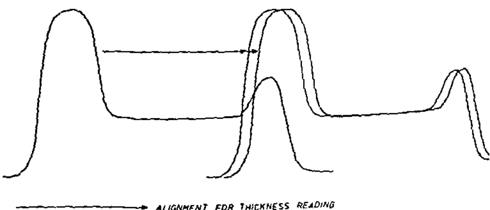


Fig 5

Model of optical conditions for thickness alignment (Scatter profile modified from McCally & Farrell (1976)) Displacement of the scatter profile in figure corresponds to the horizontal displacement of the two half images formed by the beam splitter Because the slit edge cannot be defined exactly several alignment possibilities exist

The light scattered by the cornea when sectioned by a narrow slit beam has been studied by McCally & Farrel (1976) Their results clearly illustrate the alignment conditions and the difficulties associated with a reproducible estimate of the corneal thickness (Fig 5) What is interpreted as bands in the optical section is not perfect images of the slit but rather a sinus-oidal distribution of light with no sharply defined edges When alignment of edges has to be performed the observer must decide that at a certain level of scatter he will chose this as the edge From this it seems evident that the alignment for thickness reading has a subjective component For alignment A an end to-end alignment of the image of the optical section is performed *If a very small change in light scatter from the baseline is considered as* an edge the alignment of corresponding points on both sides of the optical section would result in a high thickness reading as compared to an A alignment which defines a larger change in light scatter as the edge In alignment B a side to-side alignment of the edges of the anterior and posterior bands of the optical section is attempted The two sides are however not superimposable and again the thickness reading may vary according to which points are chosen as corresponding points on the scatter profile (examplified in Fig 5)

Not only alignment A but also alignment B was found to be slit width dependent The reason for the latter observation is not clearly understood In continuation with the considerations above it means that the corresponding points on the scatter profile are moving apart as the slit width decreases The posterior band differs from the anterior band both in intensity and in edge resolution It may be speculated that as the slit width decreases the edges of the posterior band may flatten somewhat so that if the measuring points are defined at a certain level of light scatter they will move slightly apart.

The lack of a reproducible estimate of the corneal thickness thus lies in the difficulties in exact definition of the edges of the bright bands of the optical section For the same reason it is not possible to make exact corrections for the slit width error

In order to improve the inter-observer error somewhat we suggest that the actual slit width is always measured and stated in clinical studies on the thickness of the cornea in addition to the method of alignment and slit lamp characteristics Even then the present study shows that the normal values may differ on the second decimal point Hence it would be very desirable if reproducible measuring points could be defined for the obliquely viewed optical section The present angle of observation and the optical resolution of currently available slit lamps does not allow the anterior broad band of the optical section to be divided into two minor bands produced by the slit beam as it passes through the anterior and posterior layers of the epithelium The study by McCally & Farrell (1976) suggests that this two-band resolution of the anterior band may be possible for a very narrow slit

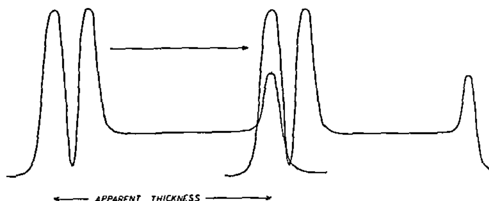


Fig 6
If the broad anterior band of the optical section could be resolved into two narrow bands, it might be possible to define a reproducible alignment method for thickness reading

and/or a large observation angle If this could be accomplished for the pachometer setting it would be possible to define the center of the anteriormost band and the center of the posterior band as corresponding measuring points (Fig 6) In this situation the thickness alignment would be unbiased by the slit width as well as observer independent Unfortunately this is not possible with present standard systems

References

Donaldson D D (1966) A new instrument for the measurement of corneal thickness *Arch Ophthal (Chicago) 76* 25–31

Ehlers N & Sperling S (1977) A technical improvement of the Haag Streit pachometer *Acta ophthal (Kbh) 55* 333–336

Jaeger W (1952) Tiefenmessung der menschlichen Vorder Kammer mit planparallelen Platten (Zusatzgerat zur Spaltlampe) *Graefes Archiv f Ophthal 153* 120–131

McCally R L & Farrell R A (1976) The depth dependence of light scattering from the normal rabbit cornea *Exp Eye Res 23* 69–81

Mishima S & Hedbys B O (1968) Measurement of corneal thickness with the Haag Streit pachometer *Arch Ophthal (Chicago) 80* 710–713

Olsen T Nielsen C B & Ehlers N (1980) On the optical measurement of corneal thickness Optical principle and sources of error *Acta ophthal (Kbh) 58* 760–766

Sokal R R & Rohlf F J (1969) Biometry W H Freeman and Company San Fransisco

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THE EFFECT OF CARBONIC ANHYDRASE INHIBITION ON CENTRAL CORNEAL THICKNESS AFTER CATARACT EXTRACTION

BY

CARSTEN BO NIELSEN

The influence of acetazolamide (a carbonic anhydrase inhibitor) on central thickness of the human cornea in vivo was studied. Corneal thickness as measured after cataract surgery was significantly increased by acetazolamide if the specular microscopy revealed central corneal guttae pre-operatively. When no guttae were seen by specular microscopy, no effect could be demonstrated.

Key words: corneal thickness – endothelium – carbonic anhydrase – acetazolamide.

Normal function of the limiting layers of the cornea is crucial for maintaining stromal hydration. The endothelium is believed to function on basis of a pump-leak theory (Mishima & Kudo 1967; Trenberth & Mishima 1968; Maurice 1972). The active component in rabbit endothelium has been characterized by dependence on bicarbonate (Hodson 1971, 1974; Dikstein & Maurice 1972) and carbonic anhydrase (Fischbarg & Lim 1974; Hodson & Miller 1976; Hull et al. 1977) for conversion of exogenous CO_2 to HCO_3^-. Silverman (1973) found carbonic anhydrase in the endothelium in the same order of magnitude as in most secretory tissues.

The previous studies were performed on rabbit corneas in vitro. The purpose of the present study was to reveal the possible significance of carbonic anhydrase activity in the human cornea in vivo.

As no effect on normal corneal thickness was found when a carbonic anhydrase

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inhibitor was administered (unpublished data) patients to be cataract extracted were chosen The post-operative condition comprising a hyperhydrated state would seem to favour the possibility of showing a decrease in the deswelling capacity of the endothelium

Patients with cornea guttata were considered a separate group These patients are seen to have a different CCT response to cataract surgery (Olsen 1980) and a higher incidence of postoperative corneal oedema (Jaffe 1976) probably as a sign of endothelial malfunction

Material and Method

Material The material comprised 55 consecutive patients with senile cataract Patients with other past or present eye disease or intraocular pressure > 21 mmHg were omitted The first 25 patients received acetazolamide and the next 30 served as control In the drug group 5 of the 25 were excluded (2 with surgical complications 2 with striate oedema leading to uncertain CCT measurements and 1 due to drug intolerance) In the control group 3 were excluded (1 with surgical complications 1 with striate oedema and 1 with post operative hyphaema)

All operations were performed with the same technique (corneal incision cryoextraction running 10–0 nylon suture) by 6 surgeons No significant difference in corneal first post operative-day thickness of the patients operated by the different surgeons could be demonstrated

Method The endothelium of all eyes to be operated on were examined by non-contact specular microscopy as described by Olsen (1979) 3–4 exposures were taken of each cornea paying attention to the possible presence of central corneal guttae Guttae were defined as round dark areas comprising defects in the endothelial reflex larger than two endothelial cells and changing in size with the focusing If more than one defect defined as above were present on either exposure the cornea was classified as guttata

Further the central corneal thickness (CCT) and intraocular pressure (IOP) were measured The CCT measurements (mean of 3 readings to the nearest 5 μm) were performed with a modified Haag Streit pachometer (Ehlers & Sperling 1977) using the technique (alignment A) described by Olsen et al (1980) with a coefficient of variation ~ 0 01 IOP was measured with applanation tonometry

Experiments The drug group included a total of 20 patients Based on the pre-operative specular microscopy 8 patients were classified as normal (age 67 1 ± 3 8 mean ± SEM) and 12 as guttata (75 1 ± 2 6) The 27 patients to serve as control comprised 14 normal (age 69 1 ± 3 6) and 13 guttata (73 0 ± 1 62)

The patients to be medicated were given acetazolamide (Diamox® Duplex Lederle) 500 mg × 2 for 3 days starting on the first post-operative day in the evening ending on the fourth day in the morning

The CCT was measured at the same time of the day pre-operatively and daily from the first to the sixth post-operative day IOP was measured pre operatively and daily from the second to the sixth post-operative day

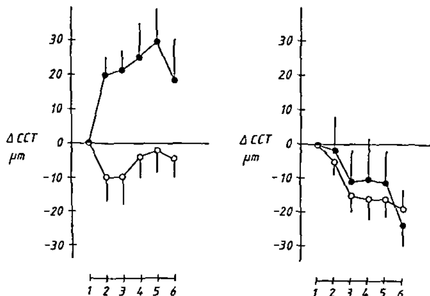


Fig 1
CCT (mean ± SEM) relative to the first post-operative-day value for the operated eye Left guttata Right normal Closed circles after acetazolamide Open circles control

Results

The aim was to test the ability of the cornea to deswell from a given thickness during simultaneous acetazolamide medication It was decided to let the individual CCT as recorded on the first post-operative day be the zero value Doing this a contamination based on interpersonal variation in CCT as measured in absolute numbers was avoided The mean increase in CCT on the 1 post-operative day relative to the pre-operative value was not significantly different from group to group (normal/drug 63 8 ± 11 1 µm mean ± SEM normal/control 70 ± 6 1 µm guttata/drug 66 6 ± 9 3 µm and guttata/control 74 6 ± 12 5 µm)

The corneal deswelling in the 4 groups are shown in Fig 1 Acetazolamide did not affect the deswelling rate of the normal corneas whereas guttata corneas actually swelled On all days were the CCT values recorded in this group greater than the value on day 1 Considering the group control/guttata a secondary rise in CCT is found on day 4 and 5 The mean CCT in the guttata/drug group are different from control by approximately 30 µm (day 1 and 2 $P < 0\ 01$ day 3 and 4 $P < 0\ 05$ t test)

The IOP on each day was not found to be significantly different between any two groups (Fig 2)

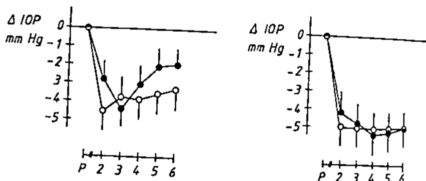


Fig 2

IOP (mean ± SEM) relative to the pre operative (P) value for the operated eye Left guttata Right normal Closed circles after acetazolamide Open circles control

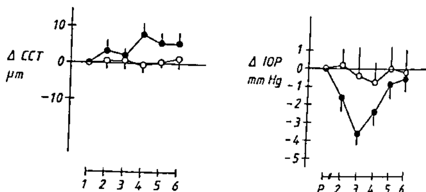


Fig 3

CCT (mean ± SEM) relative to the first post operative day value and IOP (mean ± SEM) relative to the pre operative (p) value Both recordings are for the guttata fellow non operated eye Closed circles after acetazolamide Open circles control

Fig 3 shows CCT and IOP for the non-operated fellow eye in the guttata groups CCT in the drug group is greater than control on day 4 ($P < 0.02$ t test) Between the normal groups no such significant difference was found neither considering CCT nor IOP (not shown)

Discussion

The aqueous concentration of the lipidsoluble acetazolamide in steady state is assumed to be equal to the free active fraction in plasma (Davson 1950) and so the effective concentration would be the same The dose was 7–10 mg/kg giving an

aqueous concentration of 0 5 − 1 0 × 10 5 M both in the middle of the range for sole effect on carbonic anhydrase as stated by Maren (1977) No effect of acetazolamide other than carbonic anhydrase inhibition is known for concentrations below 10^{-3} M (Maren 1977)

It was found that after systemically administered acetazolamide cornea guttatae did not retain the deswelling capacity as seen in the control group Considering the fellow non-operated guttata eye a small swelling tendency was also noted A tendency towards an IOP-drop however was seen in this case Normal corneas were not affected by acetazolamide The reason for this could be several Differences in IOP may be ruled out (Fig 2) Becker (1957) and Maren (1976) found only small changes in the aqueous plasma ratio (already nearly one) of pH Cl HCO_3 and Na^+ after acetazolamide medication changes so small that they could not explain the loss of capacity for corneal deswelling (Hodson 1971 Dikstein & Maurice 1972)

Differences in aqueous concentration of acetazolamide between normal and guttata eyes cannot be completely ruled out The relative permeability of the ciliary epithelium of cornea guttata eyes to acetazolamide is not known neither in the normal state nor when modified as after cataract surgery Further in the actual region of drug-concentration (10 5 M) the physiological response exhibits a step course so that small changes in concentration would yield greater physiological response

It seems tempting to speculate that corneae guttatae are in a state close to decompensation considering dehydration The uncatalyzed hydration of CO in aqueous is so fast (t = 5 sec Silverman 1973) that only when corneal dehydration is almost decompensated could an effect of carbonic anhydrase inhibition be expected Fuchs endothelial dystrophy exhibiting corneal guttae is a condition with frank oedema The carbonic anhydrase dependence of the pump was found to be 33−60% (Fischbarg & Lim 1974 Hodson & Miller 1976 Hull et al 1977) so partly inhibiting an active maybe nearly decompensated fluid pump may be the straw that broke the camel s back

The post-operative CCT-course of the group guttata control is seen to follow the two normal groups for the first 3 days Then a secondary rise in thickness is noted also found by Olsen (1980) After penetrating keratoplasty Bramsen & Ehlers (1979) found that not until 3 days after operation was CCT at maximum value if corneal host disease was Fuchs endothelial dystrophy suggesting some aqueous factor to be involved in the regulation of CCT

This study would seem to contradict the use of acetazolamide in the treatment of Fuchs endothelial dystrophy (Warring et al 1978)

So the results in this clinical study on the human cornea would be consistent with earlier studies on rabbit corneas in vitro that fluid transport across corneal endothelium at least partly is based on carbonic anhydrase supplying bicarbonate to a transport system

References

Becker B (1957) Chemical composition of human aqueous humor Effects of acetazolamide Arch Ophthal (Chicago) 57 793–800

Bramsen T & Ehlers N (1979) Early postoperative changes in graft thickness after penetrating keratoplasty Acta Ophthal (Kbh) 57 258–268

Davson H (1950) The penetration of some sulphonamides into the intraocular fluids of the cat and rabbit J Physiol 110 416–426

Dikstein S & Maurice D M (1972) The metabolic basis to the fluid pump in the cornea J Physiol 221 29–41

Ehlers N & Sperling S (1977) A technical improvement of the Haag Streit pachometer Acta ophthal (Kbh) 55 333–336

Fischbarg J & Lim J J (1974) Role of cations anions and carbonic anhydrase in fluid transport across rabbit corneal endothelium J Physiol 241 647–675

Hodson S (1971) Evidence for a bicarbonate-dependent sodium pump in corneal endothelium Exp Eye Res 11 20–29

Hodson S (1974) The regulation of corneal hydration by a salt pump requiring the presence of sodium and bicarbonate ions J Physiol 236 271–302

Hodson S & Miller F (1976) The bicarbonate pump in the endothelium which regulates the hydration of rabbit cornea J Physiol 263 563–577

Hull D S Green K Boyd M & Wynn H R (1977) Corneal endothelium bicarbonate transport and the effect of carbonic anhydrase inhibitors on corneal permeability and fluxes and corneal thickness Invest Ophthal Vis Sci 16 883–892

Jaffe N S (1976) Cataract Surgery and its Complications p 253 2nd ed Mosby St Louis

Maren T M (1976) The rates of movement of Na^+ Cl^- and HCO_3 from plasma to posterior chamber effect of acetazolamide and relation to the treatment of glaucoma Invest Ophthal 15 356–364

Maren T M (1977) Use of inhibitors in physiological studies of carbonic anhydrase J Physiol 291–297

Maurice D M (1972) The location of the fluid pump in the cornea J Physiol 221 43–54

Mishima S & Kudo T (1967) In vitro incubation of rabbit cornea Invest Ophthal 6 329–339

Olsen T (1979) Non-contact specular microscopy of human corneal endothelium Acta ophthal (Kbh) 57 986–998

Olsen T (1980) Corneal thickness and endothelial damage after intracapsular cataract extraction Acta ophthal (Kbh) 58 424–433

Olsen T Nielsen C B & Ehlers N (1980) On the optical measurement of corneal thickness II The measuring conditions and cources of error Acta ophthal (Kbh) 58

Silverman D N (1973) The detection and localization of carbonic anhydrase in the rabbit cornea Exp Eye Res 17 199–136

Trenberth S M & Mishima S (1968) The effect of ouabain on the rabbit corneal endothelium Invest Ophthal 7 44–52

Waring G O Rodrigues M M & Laibson P R (1978) Corneal dystrophies II Endothelial dystrophies Surv Ophthal 23 147 168

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SEMIQUANTITATIVE CYTOLOGIC ANALYSIS OF FLUID WASHED THROUGH THE LACRIMAL PASSAGE

BY

M S NORN

A quantitative cytologic analysis of the sediment of 5 ml of saline (0 9%) washed through the lacrimal drainage system of 95 normal and 84 diseased eyes revealed that the cytological picture reflects the conditions in the lacrimal passages and not in the conjunctiva
Neutrophilia was seen to become increasingly frequent with slowing down of the flow through the lacrimal passage estimated on the basis of dye dilution in the lacrimal river and dye dilution in the fluid washed through the lacrimal drainage system and also by the spontaneous passing of the dye to the nasopharynx
Neutrophilia was present in no more than 8% of normal eyes as against 69% of eyes with epiphora 83% with infectious conjunctivitis 40% with conjunctivi*tis sicca and 50% with chronic simple conjunctivitis*
Neither lymphocytosis nor eosinophilia was seen in any normal eyes
Erythrocytes were admixed artificially by washing through and probing
Granules were absent in normal eyes but present in 5% of the diseased eyes while hairs were found in 4 and 14% respectively and the fungus Alternaria in 4 and 1%

Key words cytology conjunctiva lacrimal drainage system – epiphora – vital staining rose bengal – neutrophilia

The cytology of the conjunctival fluid can be studied quantitatively e g by suction through a pipette laterally in the inferior fornix over an area of 3 14 mm² (Norn 1960) This can give us valuable clinical information Thus over 100 neutrophilic granulocytes indicate presence of bacterial conjunctivitis over 50 columnar epithelial cells pathologically increased epithelial desquamation etc

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A similar cytologic analysis of the lacrimal sac and duct seems to be worth while Therefore after washing through of the lacrimal passage the wash fluid was examined for amounts of cells The aim was 1) to examine a normal material 2) to examine a clinical material (epiphora among others) 3) to ascertain whether the cell numbers corresponded to those of the conjunctival fluid in other words whether the cells had merely passed from the conjunctiva into the lacrimal passage or the cells had been formed locally thus differing from those of the conjunctiva in type and number

Method

Washing through of the lacrimal passage was preceded by the following clinical examinations break up time (stability of the precorneal film estimated using a stop watch after vital staining by 0 125% fluorescein) Then a mixture of rose bengal and fluorescein (1% of each) was instilled The dye dilution in the lacrimal river indicating the tear flow was estimated after exactly 5 min (lacrimal river dilution test) Rose bengal staining was scored on cornea and conjunctiva according to a score system marking the degree of possible drying up (up to 30 scores gave one point less than 100 two points less than 1000 three points less than 10 000 four points and more than 10 000 five points in exposed temporal and nasal segments of the conjunctiva and on the cornea i e maximally 15 points per eye) Rose bengal vital staining along the lid margin (Marx line) and its relation to the punctum lacrimale was noted down (ectropion entropion deficient functioning)

After 10 min and again after another 10 min spontaneous passing of dye to nose and pharynx was controlled by Wood s light built into a magnifying glass in some cases following repeated intense blowing of the nose and examination of the handkerchief used

Residual vital stain was removed from the conjunctival sac by washing with salı and an anaesthetic (0 4% oxibuprocaine) was instilled Then the lacrimal p was washed through with saline if necessary after dilation of the punctum la by a conical probe

The *washing through* was performed through a thin blunt angulaı mounted on a syringe containing 5 ml of 0 9% saline The patient s hea so far forward that the wash fluid could pass direct into a kidney shaped patient s mouth was kept closed In cases with obstructed passage performed and thereafter washing

The wash fluid was centrifuged (1000 RPM for 5 min) The sedimen a drop of 10% formaldehyde dried on a slide and afterwards sta fuchsin and eosin

Regarding the individual methods including cell counting technique and mucus grading reference is made to Norn (1974 1977)

Student s t test was employed for stastical calculation of the P value

Material

A total of 109 lacrimal passages from 59 subjects were examined (35 females and 24 males ranging in age from 14 to 85 mean age 53 7)

The normal material comprised 25 lacrimal passages from 25 subjects 12 females and 10 males ranging in age from 20 to 85 mean age 49 3

The pathological material was composed as shown in Table II The 22 persons (32 eyes) with epiphora were all without rhinitis The epiphora was unilateral in 11 persons one side predominated in 7 and the resting 4 cases were equally bilaterally

Results

The cytologic sample of wash fluid from the lacrimal passage was of a reasonably good quality being suitable for estimation of cell types cell numbers and contents of mucus

Table I

Cell numbers in fluid washed through the lacrimal passage 25 normal eyes

	Number of cells				Number of lacrimal passages above upper limit (in %)
	Average	Range	10–90% percentile	normal upper limit	
Neutrophilic granulocyte	38	1–390	5–50	100	(8)
Lymphocytes	3	0 20	0–8	100	(0)
Nucleated squamous cells	13	0–93	0–28	50	(4)
Keratinised squamous cells	2	0 30	0–4	50	(0)
Cuboid epithelial cells	7	0– 9	0– 24	50	(4)
Columnar epithelial cells	1 5	0 8	0–	50	(0)

Table II

Cell numbers in fluid washed through the lacrimal passage 82 diseased eyes Average numbers of cells and in brackets percentage of lacrimal passages above upper normal limit (cf Table I)

Diagnosis	Neutrophilic granulocytes	Lymphocytes	Nucleated squamous cells	Keratinised squamous cells	Cuboid epithelial cells	Columnar epithelial cells	Number of lacrimal passages
Dacryocystitis	125 399 (88)	11 393 (25)	6 (13)	0	8 (0)	8 (0)	8
Dacryocysto-rhinostomy	4 454 (100)	142 (40)	120 (60)	8 (0)	38 (20)	0	5
Ephiphora	12 641 (69)	108 (25)	476 (50)	529 (13)	278 (38)	122 (9)	32
Entropion	21 (0)	2 (0)	3 (0)	0	2 (0)	3 (0)	4
Ectropion or lacking punctum lacrimale	90 580 (100)	2110 (67)	93 (33)	0	0	0	3
Conj sicca	283 (40)	106 (30)	222 (50)	34 (10)	99 (40)	20 (10)	10
Conj simplex	824 (50)	31 (13)	105 (50)	19 (13)	59 (25)	7 (0)	8
Conj infect	10 [illegible]5 (83)	408 (67)	315 (67)	13 (17)	50 (37)	0	6
Others*	1741 (38)	12 (0)	164 (50)	53 (13)	11 (13)	1012 (38)	8

* Others comprise papillomatous conj (2) follicular conj (2) corneal transplantation (2) and facial nerve palsy (2)

Normal eyes

The findings regarding cells in normal eyes are shown in Table 1 Generally only few cells were present but all the samples were found to contain some cells The lowest total number was three

Neutrophilic granulocytes were noticed in all cases on an average 38 cells Only two samples had more than 100 cells (320 and 150 respectively)

Lymphocytes were rarer being present in 52% most often in fairly small numbers

Epithelial cells were of the same types as in the conjunctiva cuboid epithelial cells (in 44%) columnar (in 40%) nucleated squamous cells (in 68%) and keratinized nucleated squamous cells (in 24%) The various cell types were practically always present in numbers under 50 In a few cases the columnar cells were longer than they generally are in the conjunctiva

Table I shows the upper cell number limits to be equal in quantitative pipette specimens from the conjunctiva and in the fluid washed through the lacrimal passage namely 100 for neutrophilic leucocytes and lymphocytes and 50 for each of the epithelial cell types while eosinophilic granulocytes were absent in normal eyes

Flakes of epithelial cells with coherent cells occurred in 24% Only one case (4%) had a total of over 50 cells in one sample (28 cuboid 24 squamous and 80 columnar)

Erythrocytes were seen in 64% less than 100 erythrocytes in 44% innumerable (millions) in 8% of the 25 normal eyes The washing may thus in some instances proceed without injuring blood vessels even when a conical probe is used while in others profuse haemorrhage occurs

Table III

Neutrophilia in lacrimal passage in relation to tear flow test, 109 cases The figures represent percentages of eyes with neutrophilia Normal lacrimal river dilution test defined as dilution to at least a pale orange colour within 5 min Fluid washed through the lacrimal passage is normally yellow while a more intense colour (orange red N = 42) and no colour at all (N = 13) indicate pathological conditions

	Normal	Pathological	*P*
Lacrimal river dilution test	43	64	< 0 05
Spontaneous passing of dye to nasopharynx	41	64	< 0 05
Dye in wash fluid	40	62	< 0 05

No granules were found in the wash fluid In one case (4%) coiled hairs were noticed (16 with roots presumably cilia) while fungi (seven Alternaria specimens without neutrophilia) occurred in one case only (4%)

Diseased eyes

Neutrophilia (more than 100 neutrophilic granulocytes predominating over lymphocytes) suggests bacterial infection of the conjunctiva (Norn 1974) Neutrophilia was very frequent in the fluid washed through the lacrimal passage (Table II) against in no more than 8% of the normal eyes (Table I)

As might be expected neutrophilia in the lacrimal passage was frequent and very pronounced in cases of dacryocystitis There were up to nearly one million cells a veritable lump of pus

Neutrophilia was also seen after Toti s operation indicating persisting bacterial infection in the system or nose Epiphora was associated with neutrophilia in 69% (c f 8% of normal eyes $P \leqslant 0\,001$) There was pronounced neutrophilia in ectropion and failing punctum lacrimale function whereas not so in entropion

Table III illustrates the relation between occurrence of neutrophilia and results of lacrimal river dilution tests in the total material Neutrophilia proved to be most frequent in relation to reduced tear flow obstructed spontaneous passage of dye to nose and pharynx and non-dilution of dye instilled into the conjunctiva and afterwards examined in the fluid washed through The same tendency prevailed for the group of isolated epiphora On the other hand no correlation was noticed between occurrence of neutrophilia in fluid washed through the lacrimal drainage system and break up time or rose bengal vital staining of cornea and conjunctiva

This goes to show that impeded passage through the lacrimal drainage system is attributable to neutrophilia in the region concerned

In infectious bacterial conjunctivitis neutrophilia may be present not only in the conjunctiva but also in the lacrimal passage The latter is not pronounced however nor is it always present

Conversely neutrophilia in the lacrimal passage was often seen in chronic simple conjunctivitis and keratoconjunctivitis sicca without conjunctival infection

Eosinophilic granulocytes were not detected in the tear fluid

Lymphocytes were frequently found in fairly large numbers most often concurrently with neutrophilia Proper lymphocytosis (more than 100 lymphocytes predominating over neutrophils) was demonstrated in the lacrimal passage in one case only (a case of keratoconjunctivitis sicca)

Epithelial cells in increased numbers were frequently observed in association with neutrophilia in the lacrimal passage All types were surprisingly often present in pathological numbers within the epiphora group compared with proper dacryocystitis where neutrophilic granulocytes predominated

In no more than six cases were pathological numbers of epithelial cells noticed without co-existing neutrophilia These were scattered over the various diagnostic groups (conjunctivitis sicca papillomatous conjunctivitis follicular conjunctivitis) Their occurrence seemed to be independent of probing difficulties

Epithelial cell flakes and *erythrocytes* occurred in approximately the same numbers in the individual groups as in normal eyes

Fungi In 5% bluish black coarse granules were seen toghether with neutrophilia and in one of these also Alternaria (fungus specimens) In one case (sicca) a lump was observed consisting of a thousand anuclear squamous cells

Hairs were detected in the wash fluid in 14% distributed over all diagnostic groups maximum 30 hairs in one sample This finding does not differ significantly from that in the normal material In the pathological material showing hairs the number of neutrophils was not higher than might be expected (67% with neutrophilia Average number of neutrophils per sample 7459 against total pathological material 13 967)

Relation to cytology of conjunctiva

The cytology of the conjunctival fluid of 80 eyes was analysed quantitatively before the lacrimal passage was washed through Neutrophilia was found in the wash fluid in 45% with conjunctival neutrophilia and 49% without (Table IV)

Neither was any correlation ascertained between the cell contents in the conjunctival fluid and the lacrimal passage as regards eosinophilia (three had conjunctival eosinophilia while none had lacrimal passage eosinophilia) lymphocytosis (three had conjunctival lymphocytosis *alone* and one lacrimal passage lymphocytosis *alone*) increased number of epithelial cells or mucus

Table IV

Relation between neutrophilia in conjunctiva and lacrimal drainage system estimated by quantitative cytologic pipette sample test from the conjunctiva (Norn 1974) and quantitative analysis of fluid washed through the lacrimal passage A total of 80 eyes

	Lacrimal passage	
	Normal	Neutrophilia
Conjunctiva normal	24	23
Conjunctiva neutrophilia	18	15

Colour and mucus content of fluid washed through lacrimal passage

The colour of the wash fluid was studied in the slit lamp in white light and in cobalt filtered light In 49% of the total material of 109 eyes the colour was yellow and in 39% orange or red indicating a slower passing during the experimental period In the remaining 12% the fluid was colourless (failing transfer of rose bengal fluorescein vital stain from the conjunctiva to the lacrimal passage)

Neutrophilia in the lacrimal passage was seen to be increasingly frequent the more impeded the flow 40 60 and 69% in the stated order (cf Table III)

The amount of mucus in the fluid washed through the lacrimal passage was likewise seen to increase the slower the flow Thus grade 3 mucus was found in 11% with yellow wash fluid 59% with fluid of a stronger colour and 54% with colourless fluid ($P < 0\ 01$)

The amount of mucus was increased in dacryocystitis (average grade 3 4 against the normal 1 8) epiphora (2 4) ectropion (3 3) dacryocystorhinostomy (? 8) but normal in simple conjunctivitis (1 8) and conjunctivitis sicca (1 4)

Flocculent particles sediment or milky wash fluid was found in 32 of the 109 eyes This indicates admixture of blood (more than 1 million erythrocytes in 34% against 0% in clear wash fluid $P \leqslant 0\ 001$) or neutrophilia (in 72% against 49% in clear wash fluid $P < 0\ 02$) The amount of mucus in the lacrimal passage seemed to be increased (mean grade 2 64 against 2 17 in the total material)

Discussion

The cells in the fluid washed through the lacrimal passage might be conceived simply to reflect the cytologic conditions in the conjunctival fluid Cells from the conjunctiva are to pass through the lacrimal passage just as instilled vital stain for instance

The present investigation was the first to demonstrate by a quantitative cytologic technique that the cytologic conditions in the two regions are in the main independent of each other An analysis of the cytology of the lacrimal passage can therefore give information of clinical value The normal figures for the wash fluid happened to correspond to the figures arrived at in the conjunctivo-cytologic analysis though the areas differed (the hollow space of the lacrimal passage and part of the nose *versus* 3 mm² conjunctival area)

A reduced flow will raise the cell number in the lacrimal passage despite an unchanging cell production the cells being removed at a slower rate However this cannot alone explain the great variations noticed in the present study because some cases were seen with very few cells despite arrested flow and others with many cells

despite unimpeded flow and passage The percentage distribution of cells also varied appreciably

The most important cytologic finding is that of neutrophilia The clinical material showed the degree of neutrophilia to rise with decreasing tear flow Neutrophilia indicates bacterial infection One gets the impression that repeated infections in the lacrimal passage cause neutrophilia which will impede the flow This gives rise to bacterial re infection with neutrophilia resulting in further slowing down of the flow Moderate epiphora will thus proceed to becoming pronounced epiphora which perhaps gradually will develop into proper dacryocystitis

In assessing the wash fluid sample cytologically we must therefore attach importance to the finding of neutrophilia which indicates bacterial infection of the lacrimal drainage system Antibiotic treatment by washing (or conjunctival instilla tion) is recommended

Finding of fairly large granule formations suggest presence of tear stones (fungi) Large amounts of epithelial cells may presumably obstruct the passage through the system We can hardly attach any importance to observation of hairs the fungus Alternaria or erythrocytes (cf findings in normal eyes mistaken hairs from the nose and regarding erythrocytes mechanical damage by washing)

Examination of the wash fluid may be of value even without cytologic analysis provided it has been preceded by rose bengal fluorescein vital staining of the conjunctiva

Dilution of the wash fluid to yellow colour indicated good function to orange or red colour impeded flow and no colour occluded lacrimal drainage system Flocculent particles suggest neutrophilia or admixture of blood

Cytologic analysis gives further details Larger clinical materials can clarify the significance of lymphocytosis (cf Coster et al 1979) and eosinophilia in the lacrimal drainage system

References

Coster D J & Welham R A N (1979) Herpetic canalicular obstruction *Brit J Ophthal 63* 259–262

Norn M S (1960) *Cytology of the conjunctival fluid Acta ophthal (Kbh.) Suppl 59* 159

Norn M S (1974) External Eye Methods of Examination p 200 Scriptor Copenhagen

Norn M S (1977) Outflow of tears and its influence on tear secretion and break up time (BUT) *Acta ophthal (Kbh) 55* 674–682

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HLA ANTIGENS IN CASES OF GIANT CELL ARTERITIS

BY

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and F KISSMEYER NIELSEN

HLA tissue type antigen determination for A B and C antigens in 88 patients suffering from giant cell arteritis of the temporal artery showed no significant deviations as compared to a control material of 3164 blood donors A weak indication of association with antigen HLA B8 appeared to be of interest due to a corresponding indication in a previous investigation The patients were a mixed hospital material consisting of cases of clinical temporal arteritis and patients with polymyalgia rheumatica There was an overrepresentation of women (77%) Familial occurrence was demonstrated sporadically (3 pairs of siblings)

Key words giant cell arteritis – temporal arteritis – polymyalgia rheumatica – HLA antigens – familial occurrence

The etiology of giant cell arteritis is unknown An immune reaction is a possibility (for a survey see Hunder & Allen 1978) The HLA antigenic determinants in the cell membranes are considered as being related to cell recognition and immunological response (Bodmer 1972) In addition it is considered that the genes on

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chromosome No. 6 are closely linked to immune response genes. Population studies regarding association between HLA antigens and immune related diseases are therefore of interest. Terasaki et al. (1976) and Hunder et al. (1977) were unable to demonstrate association in 9 and 43 patients with giant cell arteritis respectively. Seignalet et al. (1977) found an increased occurrence of HLA B14 in 61 patients ($P = 0.002$), while Hazleman et al. (1977) found that HLA B8 occurred more frequently in 30 patients suffering from giant cell arteritis ($P = 0.02$) as well as in 27 patients with polymyalgia rheumatica ($P = 0.002$) where the artery biopsy was negative.

Material

The material comprises 88 unrelated patients (66 women, ages 58–100, average 75 years, and 22 men, ages 57–87, average 75 years). These patients had been admitted to a Danish hospital, either the medical or ophthalmological departments, during the period 1974–1979. Histological examination of the temporal artery or one of its branches revealed arteritis compatible with the diagnosis giant cell arteritis (histopathological criteria as described by Hunder et al. (1975)).

Nineteen patients had the clinical diagnosis polymyalgia rheumatica, where a biopsy had demonstrated giant cell arteritis of the temporal artery. Sixty-nine patients had clinical symptoms of temporal arteritis. Unilateral severe reduction in vision was a symptom in 18 patients, while this was present in both eyes in a further four. In 59 patients a diagnosis of giant cell arteritis was made during admission to a medical department, and in 29 patients in the ophthalmological department.

Method

Blood samples were withdrawn during admission to hospital or in the outpatient clinic. In a number of cases the patients were requested to attend the clinic for blood sampling, and in seven other cases these were withdrawn at home. The results of the HLA typing were compared to those of a control material consisting of 3164 blood donors (1016 donors for C antigens). HLA type determination was carried out according to the method of Kissmeyer-Nielsen & Kjerbye (1967). Two × two tables for the individual antigens were evaluated by means of Fisher's test (one sided).

Table I

Frequency of phenotypes in patients and the control population Giant cell arteritis (N=
Control (N=3164) P (Fisher)

HLA antigen	Number	%	Number	%	
A1	27	30 7	993	31 4	0 496
A2	49	55 7	1690	53 4	0 378
A3	27	30 7	870	27 5	0 91
A9	10	11 4	554	17 5	0 089
A10	11	12 5	285	9 0	0 179
A11	3	3 5	331	10 5	0 015
A28	6	6 8	278	8 8	0 340
Aw19	25	28 4	595	18 8	0 0 0
B5	12	13 6	349	10 8	0 245
B7	21	23 9	911	28 8	0 188
B8	28	31 8	731	23 1	0 041
B12	14	15 9	794	25 1	0 029
B13	5	5 7	133	4 2	0 317
B14	2	2 3	123	3 9	0 334
B18	6	6 8	234	7 4	0 593
B27	13	14 8	266	8 4	0 035
Bw15	13	14 8	566	17 9	0 276
Bw16	5	5 7	165	5 2	0 491
Bw17	5	5 7	259	8 2	0 268
Bw21	1	1 1	104	3 3	0 215
Bw22	2	2 3	111	3 5	0 403
Bw35	9	10 2	414	13 1	0 274
Bw40	24	27 3	579	18 3	0 027
			(N=1016)		
Cw1	3	3 5	49	4 8	0 399
Cw2	15	17 0	96	9 4	0 024
Cw3	33	37 5	346	34 1	0 293
Cw4	8	9 1	139	13 7	0 145

Results

Table I shows the results Five antigens (HLA Aw19 −B8 −B27 −Bw40 and −Cw2) showed increased values in the present patients ($0\ 05 > P > 0\ 01$) while two antigens showed decreased values (HLA A11 and −B12) If the P values are corrected by multiplication by the number of studied properties (27) then the differences are not significant

The first patient to be studied was one of a monozygotic pair of twins both of whom suffered from giant cell arteritis (Kemp 1977 *the twins are only counted as* one patient in the present material) Further two cases of familial occurrence of the disease complex were observed A 77 year-old woman included in the present material had a sister (deceased) who had developed severe temporal arteritis with bilateral loss of vision some seven years earlier One 70-year old woman also included in the material had an older sister with polymyalgia rheumatica but no histologically verified arteritis Information was obtained regarding the above relatives from the hospital to which they had been admitted

Discussion

HLA B8 has previously been demonstrated as occuring more frequently in patients with temporal arteritis and polymyalgia rheumatica The International HLA and Disease Registry in Copenhagen has incorporated the present data in a new combined analysis (1979) It was found that for HLA B8 in 222 patients with giant cell arteritis (the 9 patients of Terasaki et al are not included) there was a relative risk of the disease in the antigen bearers equalling 1 56 ($P = 0\ 003$) Svejgard & Ryder (1977) state however that the significance limit in connection with combined analyses should be as low as 0 0004 in order to avoid false associations Thus it is only an indication

The present material includes 19 patients with the clinical diagnosis of polymyalgia rheumatica It was impossible to determine retrospectively how many of the patients with clinical temporal arteritis suffered initially from symptoms of polymyalgia Both of the diseases are in all probability cardinal manifestations of a generalized giant cell arteritis (Sørensen & Lorenzen 1977)

The frequency of giant cell arteritis in the Danish population is increasing (Kemp 1977) but awareness of the disease has also increased since 1934 (Horton et al 1934) Classical hereditary studies are not possible as the disease has only been registered for the last 45 years Further very few suffer from the disease before the age of 50 years Liang et al (1974) have in connection with their report of four pairs of closely related patients suggested that there are unknown genetic factors which predispose elderly individuals to polymyalgia rheumatica and temporal arteritis Up to the present it has been impossible to demonstrate any definite connection between such factors and the HLA system

Acknowledgment

The authors wish to thank the medical and ophthalmological departments in Esbjerg and Kolding as well as the medical departments of the hospitals in Faborg Odense and Ribe all of which have kindly put patients at the disposition of the authors for study

References

Bodmer W F (1972) Evolutionary significance of the HL A system *Nature 237* 139–145 & 183

Combined analysis from the HLA and Disease Registry Tissue Typing Laboratory University Hospital Copenhagen (1979) Unpublished data

Hazleman B Coldstone A & Voak D (1977) Association of polymyalgia rheumatica and giant cell arteritis with HLA B8 *Brit Med J 2* 989–991

Horton B T Magath T B & Brown G E (1934) Arteritis of the temporal vessels A previously undescribed form *Arch intern Med 53* 400–409

Hunder G C Sheps S G Allen C L & Joyce J W (1975) Daily and alternate-day corticosteroid regimes in treatment of giant cell arteritis *Ann Int Med 82* 613–618

Hunder C C Taswell H F Pineda A A & Elveback L R (1977) HLA antigens in patients with giant cell arteritis and polymyalgia rheumatica *J Rheum 4* 321–323

Hunder C C & Allen C L (1978) Giant cell arteritis Review *Bull rheum Dis 19* 980–986

Kemp A (1977) Monozygotic twins with temporal arteritis and ophthalmic arteritis *Acta ophthal (Kbh) 55* 183–190

Kissmeyer Nielsen F & Kjerbye K E (1967) Lymphocytotoxic microtechnique purification by flotation Report of a conference and workshop Torino and Saint Vincent Italy Munksgaard (Copenhagen) pp 381–383

Liang C C Simkin P A Hunder C G Wilske K R & Healey L A (1974) Familial aggregation of polymyalgia rheumatica and giant cell arteritis *Arthr Rheum 17* 19–24

Seignalet J Janbon C Sany J Janbon F Bidet J M Brunel M Jourdan J & Busiere J L (1977) HLA in temporal arteritis *Tissue Antigens 9* 69

Svejgaard A & Ryder L P (1977) Associations between HLA and disease In HLA and Disease Eds (J Dausset & A Svejgaard) Munksgaard (Copenhagen) 46–71

Sørensen S S & Lorenzen I (1977) Giant cell arteritis temporal arteritis and polymyalgia rheumatica *Acta Med Scand 201* 207–213

Terasaki P I Healey L A & Wilske K R (1976) Distribution of HLA haplotypes in polymyalgia rheumatica *New Engl J Med 295* 905

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THE COLOUR OF THE OPTIC DISC
VARIATION WITH LOCATION OF ILLUMINATION

BY

PER NELLEMANN SØRENSEN

The variation of the colour of the ı ⊣ was examined w th a slit lamp and contact lens in 200 normal subject ı l mo ing the image of the slit across the optic disc This event was photogr ı ı ed ı ı 15 subjects and colour densitometry was performed The temporal part of th pale central excavation changes colour to red when illuminated nasally and vice ersa
The colour change could not be p ovoked in subjects w th nc rmal discs with flattening of the temporal disc sector The whole neurorim reddens the whole way round when the lit hits the optic disc border and dependent on fundus pigmentation slight redness was produced even when the lit was placed outside the disc in the neighbourhood of the border

Key words central excavation – colour change – m crodensitometry – optic disc colour

The colour of the optic disc is still an important clinical landmark in ophthalmology since it is explicit correlated to the visual function (Cogan 1966 Walsh & Hoyt 1969) It is well known that the colour of the optic disc changes with the colour temperature of the light source (Miller & George 1978) and the age of the lens (Said & Weale 1959 Snydacker 1964) It is also known that colour changes with the incident angle from the light source Since the importance of this fact is only briefly mentioned in the literature (Kronfeldt 1967 Schwartz 1973) we have studied this phenomenon with the aid of a slit lamp and a contact lens simply by moving the image of the slit across the optic disc in 15 cases photographs of this procedure were analyzed in a densitometer

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Materials and Methods

200 normal subjects (age 6–87 mean 42 refractive error less than ± 3 diopt) had both of their optic discs examined in the Haag Streit or Rodenstock slit ... employing a Goldmann fundus contact lens When the image of the slit was mov... horizontally or vertically across the disc the colour (redness) of the illuminated ar... and of the rest of the disc was noted as well as the point at which the disc first bega... to redden when the slit was moved towards and across the border

Fifteen cases with cup disc ratio from 0 2 to 0 5 (estimated by colour contrast were photographed (Zeiss photoslitlamp magnification × 2 Flash setting IV 3... Wsec slit 0 5 mm aperture 32 slit 3 Kodachrome 64) The transmission densit... the diapositive was measured on the temporal slope of the optic disc excavation corresponding to an area with diameter 100 μ The density was read on a Reicher microdensitometer in the green (540 nm) and red (640 nm) locus where the luminousity is highest and where the unwanted absorption from overlapping between the colour forming pigments is lowest. The density in the blue was not measured since it could be demonstrated in white areas only The differences between the densities at 640 nm and 540 nm is taken as an arbitrary index of the red colour The density at 640 nm denotes the colour hue and the density at 540 nm denotes the correction factor for variation in exposure

Thus linearity exists between density and the logarithm to the exposure in the proper exposure range of the film for both green and red and furthermore the characteristic curves for green and red have practically identical slopes Variation in exposure will therefore affect the densities in the same direction The linearit... requirement is not totally fulfilled in the bright parts of the film a fact that i... considered of minor importance

Results

Slit illumination of the optic disc results in a l... neuronim i e the peripheral part of the non exc... happens as soon as the slit image hits the optic dis...

In most subjects (92%) also the central ph... contralateral side of the optic cup Thus illu... temporally and vice versa Most effective was due to the larger area of the optic cup neuronim on the nasal side

In 6% of the subjects the excavation onl... temporally These subjects had tempora... nasal displacement of the vessels

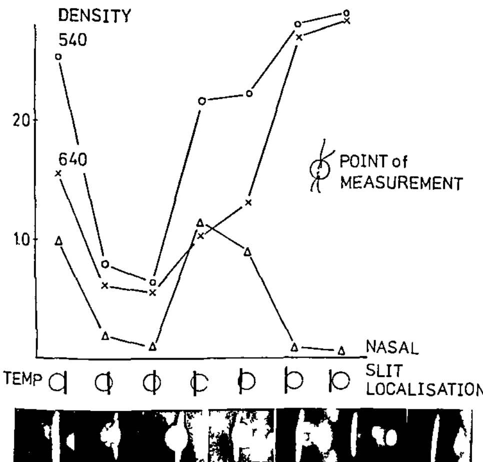


Fig 1

The redness of the central excavation as an illuminated slit moves stepwise across the left optic disc. Black and white prints of the colour diapositives in which density measurements was made is seen below. The red ×——× (640 nm) and green o——o (540 nm) density is given (arbitrary units). The difference Δ——Δ is an index of the redness

In all subjects the red glowing could also be provoked by moving the slit in the vertical direction

No difference between left and right eye could be demonstrated in any subject

In 35% of the subjects the optic disc begins to redden before the slit image reaches the border. These subjects were predominantly blonds with sparse fundus pigmentation. Thus 41% of the optic discs in blonds reacted in this way, compare

Materials and Methods

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Results

Slit illumination of the optic disc results in a light spreading effect of the whole neurorim i e the peripheral part of the non-excavated part of the optic disc This happens as soon as the slit image hits the optic disc border

In most subjects (92%) also the central physiological pallor turns red on the contralateral side of the optic cup Thus illumination nasally causes reddening temporally and vice versa Most effective was disc illumination from the nasal side due to the larger area of the optic cup and perhaps due to a more bank like neurorim on the nasal side

In 6% of the subjects the excavation only glows when illuminated nasally but not temporally These subjects had temporal flat bright but normal optic discs with nasal displacement of the vessels

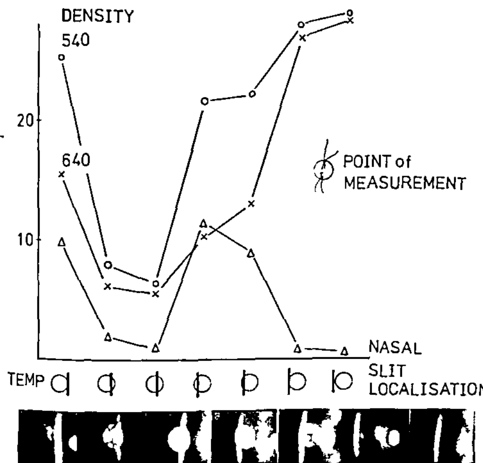


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Fig 2
Slit lamp photo of the optic disc The central excavation is white at the temporal side but red at the nasal side



Fig 3
Slit lamp photo of the same optic disc The central excavation is now red temporally No light spreading outside the optic disc is seen

to 19% of the optic discs in dark haired However the reddening was always most pronounced when the slit image reached the border of the neuronm

Fig 1 demonstrates the colour change of the temporal part of the optic cup when the slit image si moved across the optic disc in a typical record of a subject with well developed optic cup The mean redness of the temporal excavation when the slit image is placed on the nasal neuronm is 0 96 (range 0 71 − 1 10 n = 15) The redness is given by the numerical difference between the densities of the film at 640 nm and 540 nm (arbitrary units)

From Fig 1 it is seen that the optic cup redden [illegible] slit illumination both on the temporal border and also by nasal illumination

Fig 2 and 3 are colour prints of diapositives of [illegible] ur change of the central excavation when the slit image is placed tempor [illegible] [illegible] and nasally (Fig 3) Light spreading in the retina is minimal compared to that [illegible] optic disc

Discussion

This investigation has shown that the optic disc colour depends on the location of the incident light on the disc The demonstrated colour change of the physiological excavation of the disc from pale to red when the slit image is moved across the disc is puzzling Quigley & Anderson (1977) in a histopathological study on monkey eyes with descending optic atrophy considered the optic nerve fiber bundles and their adjacent glial columns as optic pathways According to them light is transferred to the optic disc longitudinal to the nerveous fibres and adjacent glias cells and later diffused among the capillaries from which the reflected light takes its pink colour The contralateral reddening of the central excavation however is difficult to explain in this way On the other hand Gloster (1972 1973) in his study of optic discs onto which a grid shadow was projected through a fundus camera explains the light transfer of the optic disc tissue as an effect of a diffusing of light projected onto it

Still the nature of the colour change from pale to red of the contralateral part of the central excavation is obscure This phenomenon might be either a guidance or a reflection of red light originating from the vascular structures of the disc tissue Another possibility could be that the colour change is due to an unveiling of underlying vascularity hitherto hidden by veiling reflections from tissue in front of it, just as the vascularity of the central excavation and apparently pale temporal parts of the optic disc is disclosed by fluorescein angiography (Hayreh 1969 1972)

When light reaches a borderline surface two possibilities exist dependent on the angle of incidence Light can either be reflected or refracted Reflection can be

specular or scattered according to the properties of the surface In transparent media refractive index differences determine the degree of refraction Thus the redness of the optic disc must depend on whether light is scattered or reflected from the surface of penetrates the tissue until it is absorbed or finally reflected from the lamina cribrosa

The optical properties of the optic disc are not known in detail and need further investigations

The described dependence of optic disc colour on different location of the illumination of the disc has great clinical importance Schwartz (1973) advocates examination of the optic disc to be done with the aid of a contact lens and the slit lamp Par example with the direct ophthalmoscope the optic cup is estimated larger

Better understanding of the colour of the optic disc colour is achieved when considering the light reflected from the optic disc tissue as an information on what transformation the light undergoes when it strikes the optic disc texture

References

Cogan D C (1966) Neurology of the Visual System Springfield III Charles C Thomas Pbl

Closter J (1973) Colorimetry of the optic disc *Trans ophthal Soc U K 93* 249–949

Gloster J (1972) Concerning glaucomatous changes at the disc in Proc 2nd William Mackenzie Memorial Symp Glasgow 1971 Published in The Optic Nerve pp 298–303 J S Cant (Ed) H Kimpton Publishers London

Hayreh S S (1969) Blood supply to the optic nerve head and its role in optic atrophy glaucoma and oedema of the optic disc *Brit J Ophthal 53* 721–748

Hayreh S S (1972) Colour and flourescense of the optic disc *Ophthalmol gica 165* 100–108

Kronfeldt P C (1967) The optic nerve In Symp on Glaucoma Trans New Orleans Acad Ophthal pp 62–73 C V Mosby St Louis

Miller N R & George T W (1978) Monochromatic photography and ophthalmoscopy of the peripapllary retinal nerve fiber layer *Invest Ophthal 17* 1121–1124

Quigley H A & Anderson D R (1977) The histologic basis of optic disc pallor in experimental optic atrophy *Amer J Ophthal 83* 709–717

Said F S & Weale R A (1959) The variation with age of the spectral transmississivity of the living human crystalline lens *Gerontologica 3* 213–231

Schwartz B (1973) Cupping and pallor of the optic disc *Arch Ophthal (Chicago) 89* 272–247

Snydacker D (1964) The normal optic disc Ophthalmoscopic and photographic studies *Amer J Ophthal 58* 958–961

Walsh F B & Hoyt W F (1969) Clinical Neuro Ophthalmology 3rd ed Williams & Wilkins Baltimore

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PULSED DOPPLER ULTRASOUND FOR MEASURING BLOOD FLOW VELOCITY IN THE HUMAN OPHTHALMIC CIRCULATION

BY

SIGMUND KVERNES SIGMUND BLIKA JAN GILTVEDT KNUT MATRE
KJELL KRISTOFFERSEN ARNE GRIP and ALF O BRUBAKK

This study was performed in order to develop a method for studying blood flow in the ophthalmic circulation Using a pulsed doppler system utilizing an ultrasonic frequency of 10 MHz blood flow velocities have been measured in the ophthalmic artery and in the arteries behind the eyeball (lateral posterior ciliary arteries) in 40 normal subjects The mean of the peak systolic velocities were 34 ± 6 cm/s in the ophthalmic artery and 14 ± 3 cm/s in the lateral posterior ciliary arteries We conclude that blood flow velocities can be measured in defined vessel areas in the orbit

Key words ophthalmic artery – posterior ciliary arteries – blood flow velocities – pulsed doppler ultrasound

Using fluorescein photographic and photometric techniques blood flow in retinal arteries can be studied (Hickam & Frayser 1966 Niesel & Gassmann 1972)

Relative changes in blood flow to the eye *in cases of carotid stenosis have been* studied using ocular pulse amplitude (Hørven et al 1971) Only indirect measurement of blood flow can be performed in this way as changes in ocular volume and compliance will influence the result

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specular or scattered according to the properties of the surface In transparent media refractive index differences determine the degree of refraction Thus the redness of the optic disc must depend on whether light is scattered or reflected from the surface of penetrates the tissue until it is absorbed or finally reflected from the lamina cribrosa

The optical properties of the optic disc are not known in detail and need further investigations

The described dependence of optic disc colour on different location of the illumination of the disc has great clinical importance Schwartz (1973) advocates examination of the optic disc to be done with the aid of a contact lens and the slit lamp Par example with the direct ophthalmoscope the optic cup is estimated larger

Better understanding of the colour of the optic disc colour is achieved when considering the light reflected from the optic disc tissue as an information on what transformation the light undergoes when it strikes the optic disc texture

References

Cogan D G (1966) Neurology of the Visual System Springfield III Charles C Thomas Pbl

Gloster J (1973) Colorimetry of the optic disc *Trans ophthal Soc U K 93* 242–249

Gloster J (1972) Concerning glaucomatous changes at the disc in Proc 2nd William Mackenzie Memorial Symp Glasgow 1971 Published in The Optic Nerve pp 298–303 J S Cant (Ed) H Kimpton Publishers London

Hayreh S S (1969) Blood supply to the optic nerve head and its role in optic atrophy glaucoma and oedema of the optic disc *Brit J Ophthal 53* 721–748

Hayreh S S (1972) Colour and flourescense of the optic disc *Ophthalmologica 165* 100–108

Kronfeldt P C (1967) The optic nerve In Symp on Glaucoma Trans New Orleans Acad Ophthal pp 62–73 C V Mosby St Louis

Miller N R & George T W (1978) Monochromatic photography and ophthalmoscopy of the peripapllary retinal nerve fiber layer *Invest Ophthal 17* 1121–1124

Quigley H A & Anderson D R (1977) The histologic basis of optic disc pallor in experimental optic atrophy *Amer J Ophthal 83* 709–717

Said F S & Weale R A (1959) The variation with age of the spectral transmississivity of the living human crystalline lens *Gerontologica 3* 213–231

Schwartz B (1973) Cupping and pallor of the optic disc *Arch Ophthal (Chicago) 89* 272–277

Snydacker D (1964) The normal optic disc Ophthalmoscopic and photographic studies *Amer J Ophthal 58* 958–964

Walsh F B & Hoyt W F (1969) Clinical Neuro-Ophthalmology 3rd ed Williams & Wilkins Baltimore

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PULSED DOPPLER ULTRASOUND FOR MEASURING BLOOD FLOW VELOCITY IN THE HUMAN OPHTHALMIC CIRCULATION

BY

SIGMUND KVERNES SIGMUND BLIKA JAN GILTVEDT KNUT MATRE KJELL KRISTOFFERSEN ARNE GRIP and ALF O BRUBAKK

This study was performed in order to develop a method for studying blood flow in the ophthalmic circulation Using a pulsed doppler system utilizing an ultrasonic frequency of 10 MHz blood flow velocities have been measured in the ophthalmic artery and in the arteries behind the eyeball (lateral posterior ciliary arteries) in 40 normal subjects The mean of the peak systolic velocities were 34 ± 6 cm/s in the ophthalmic artery and 14 ± 3 cm s in the lateral posterior ciliary arteries We conclude that blood flow velocities can be measured in defined vessel areas in the orbit

Key words ophthalmic artery – posterior ciliary arteries – blood flow velocities – pulsed doppler ultrasound

Using fluorescein photographic and photometric techniques blood flow in retinal arteries can be studied (Hickam & Frayser 1966 Niesel & Gassmann 1972)

Relative changes in blood flow to the eye in cases of carotid stenosis have been studied using ocular pulse amplitude (Hørven et al 1971) Only indirect measurement of blood flow can be performed in this way as changes in ocular volume and compliance will influence the result

Methods based on continuous wave ultrasound and the doppler principle have been proposed for studying ocular blood flow (Tokoro 1972 Yamamoto 1975)

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These methods do not permit range resolution and therefore can not give a defined sample volume with respect to depth

The method presented in this paper has been based on pulsed doppler ultrasound which permits range resolution and hence measurement of blood flow velocities of selected depths Furthermore the size of the sample volume has been experimentally determined By this method it is possible to measure blood flow velocities more accurately in the ophthalmic and the posterior ciliary arteries

In this study the feasibility of the method has been demonstrated and the reproducibility of the measurements as well as the range of normal velocities have been documented

Methods

When ultrasound is transmitted into the body the soundwaves are scattered from inhomogenities in the tissue and in the blood The frequency shift (doppler shift f_d) in reflected waves is proportional to the velocity (v) of the scatterers according to the formula

$$f_d = 2 f_0 \frac{v}{c} \cos \Theta$$

where f_0 is the frequency of the transmitted soundwaves c is the sound velocity in the tissue and Θ is the angle between the soundbeam and the path of the scatterers

By pulsing the transmitted waves and detecting the backscattered soundwaves at a given time interval after transmission depth resolution is achieved (Baker 1970)

The ultrasonic doppler velocity meter used in this study has been described in detail (Angelsen & Brubakk 1976) and only its main features will be given here

The ultrasonic frequency is 10 MHz The repetition frequency was 19 5 kHz and a pulse length of 3 microseconds gives a sample length of 4 6 mm The ultrasonic transducer acts both as a transmitter and as a receiver The backscattered ultrasound is split into two channels by a quadrature demodulator in order to separate forward from backward flow

In order to remove signals from slowly moving tissues a high pass filter with a cut off frequency of 290 Hz was used The low pass filter has a cut off frequency of 9 3 kHz to remove high frequency noise

Using analogue estimators described earlier (Angelsen & Brubakk 1976 Brubakk et al 1977) the mean and maximum velocity in the sample volume can be displayed However due to the poor signal/noise ratio when measuring from the posterior ciliary arteries analogue estimation is difficult and the received signals were analyzed using a frequency analyzer This instrument is based on a z-chirp algorithm implemented by analogue shift registers (Reticon Corp Sunnywhale USA)

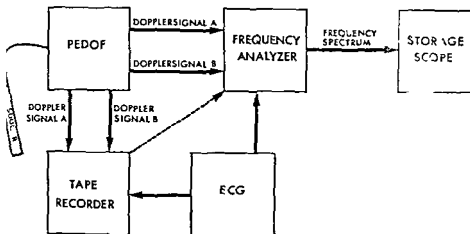


Fig 1

\ schematic view of the signal processing equipment. PEDOF Pulsed Echo-Doppler Flowmeter is developed at the Division of Engineering Cybernetics Uni ersity of Trondheim

In order to improve the time resolution of the received signals curves from about ten cardiac cycles were superimposed on an oscilloscope screen using the subject s electrocardiogram as a trigger The maximum velocity has been given by the envelope around the frequency spectrum

A schematic representation of the equipment used is shown in Fig 1

Initially we tested a transducer fastened inside a gonioscopic lens hoping that this would facilitate aiming of the ultrasonic beam by simultaneous observation of the retina through a slit lamp However this was not the case firstly because of an unavoidable pressure on the cornea secondly because of reduced mobility of the transducer All measurements in this paper have therefore been done with a rodshaped transducer made of lead zirconate-titanate (Trade Mark PZT 5A Brush Clevite) The transducer is quadratic (3 mm) and is backed by araldite The transducer has an acoustic output power of 28 mW/cm² an efficiency of 12% a phase distortion of 2% and an impedance of 17Ω

The output power of the transducer was measured by transmitting the ultrasonic beam into an absorber and detecting the ultrasonic energy by a sensitive balance weight (Mettler H L 52) The principle of this method had been described elsewhere (Kosoff 1965 Matre 1979)

The acoustic field from the transducer was measured in water (Engan 1978) The field was detected by another 10 MHz transducer having a small aperture (0.5 mm) in front of it The rod transducer was scanned in the x-direction and in the

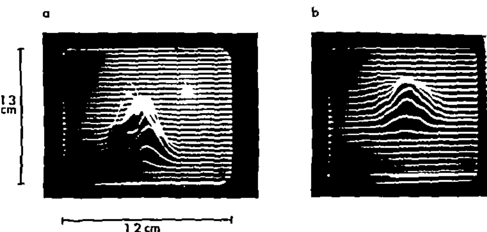


Fig 2

A three dimensional representation of the ultrasonic field of the rodshaped transducer in water The field from the 10 MHz transducer is detected by scanning a 10 MHz rod transducer of same type with a 0 5 mm aperture in front in a plane 90 to the beam. a) 1 cm from the crystal b) 3 cm from the crystal

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Fig

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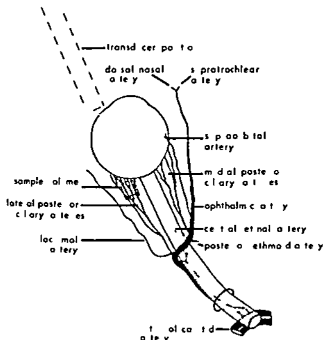


Fig 4

The most common pattern of some of the branches of the ophthalmic artery The sample volume is located lateral to the optic nerve 24 to 28 mm behind limbus cornea corresponding to the lateral main bundle of the posterior ciliary arteries The size of the volume is estimated to be 4 6 mm long and 4mm in diameter The direction of the transducer is indicated parallel to the optic nerve Redrawn after Hayreh S S (1976)

)-direction simultaneously Fig 2 shows a three-dimensional representation of the sound field in a plane 90 to the ultrasonic beam in water at two different depths

Blood flow velocity was measured in 40 subjects with no history of cardiovascular or eye diseases 16 women and 24 men (mean age 36 years range 15–70 years)

Nobody was using any drug at the time of the investigation The procedure was carefully explained to every subject and consent for doing the study was obtained All measurements were performed with the subjects in a supine position from the following sites Left and right ophthalmic artery and left and right arteries behind the eyeball (later called lateral posterior ciliary arteries)

In order to measure flow velocities in the ophthalmic artery the transducer was positioned on the nasal part of the closed upper eyelid Using methylcellulose as a coupling agent it is possible to measure without exerting any pressure on the tissue The transducer was moved until maximum velocity was obtained

The strongest signals were found at approximately 8 mm depth in all subjects. Probably this will occur just before the division of the ophthalmic artery into the supratrochlear and the dorsal nasal artery (Hayreh S S 1962) The approximate location of the sample volume in relation to the vessels can be seen from Fig 3

In order to measure the velocities in the lateral posterior ciliary arteries eye movements must be eliminated therefore the subjects were asked to focus a black spot in the ceiling The cornea was anesthetized with oxybuprocain chloride 0 4% eye drops To avoid sound absorption in the cornea and in the lens the transducer was placed at the limbus cornea in a direction approximately parallel to the optic nerve axis (Fig 4) and the position was changed until the strongest signals were detected usually from a depth of 26 mm behind the corneal limbus

Adequate signals however could be detected at depths from 24 to 28 mm Using methylcellulose no pressure was needed to obtain acoustic contact with the eyeball

In order to demonstrate changes in flow following alteration of the intraocular pressure measurements were performed using different weights on the cornea (35–120 g)

Results

Typical velocity spectra from the common carotid artery the ophthalmic artery and the lateral posterior ciliary arteries are shown in Fig 5 Each spectrum is a superimposition of about 10 cardiac cycles from a normal subject 30 years of age

The peak systolic velocities found in the ophthalmic artery and the lateral posterior ciliary arteries in 40 normal subjects have been shown (Table I)

The mean of the peak systolic velocities have been grouped according to age No significant difference in maximum systolic velocities were found with increasing age The form of the maximum velocity curve however changed with increasing age (Fig 6)

In Fig 7 histograms of the peak systolic velocities have been shown The velocities ranged from 21 to 50 cm/s in the ophthalmic arteries and from 10 to 25 cm/s for the lateral posterior ciliary arteries

In Table II the mean of the peak systolic velocities from each of 3 normal subjects measured 10 times weeks apart is presented

Fig 8 shows the effect on blood flow velocities in the lateral posterior ciliary arteries when intraocular pressure was changed The velocity spectrum in Fig 8a was recorded at normal intraocular pressure

In Fig 8b and 8c the intraocular pressure was increased for 30 seconds by placing an external weight 35 g and 60 g respectively on the cornea With increasing intraocular pressure the maximum flow velocities were reduced especially its diastolic part After release of the pressure (Fig 8d) the velocity spectrum was

slightly increased as compared to Fig 8a where normal flow conditions were to be expected Weights of 90 g and 120 g were also tried However no flow could be registrated in the posterior ciliary arteries

In the ophthalmic artery the change of intraocular pressure led to no measurable velocity changes

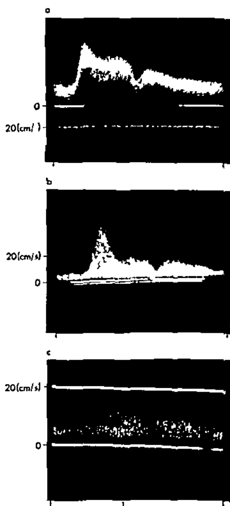


Fig 5

Velocity spectrum averaged over about 10 cardiac cycles for a) the commen carotid artery 15 mm below th skin surface b) the ophthalmic artery 8 mm below the skin surface c) lateral posterior ciliary arteries 26 mm behind limbus corneae

Table I

Mean SD and variation coefficient of the peak systolic velocities in the ophthalmic arteries 8 mm below skin surface and in the arteries 26 mm behind the corneal limbus (lateral posterior ciliary arteries) from 40 normal subjects grouped according to age

No	Age range	Mean SD and variation coefficient of the peak systolic velocities (cm/s)							
		Ophthalmic artery				Lateral posterior ciliary arteries			
		Right side		Left side		Right side		Left side	
9	(15–25)	36 ± 8	22%	33 ± 8	24%	16 ± 2	12%	15 ± 3	20%
8	(26–30)	34 ± 7	20%	34 ± 5	15%	13 ± 1	8%	13 ± 1	8%
8	(31–35)	32 ± 4	13%	33 ± 4	12%	14 ± 2	14%	14 ± 1	7%
7	(36–45)	37 ± 7	19%	36 ± 6	17%	14 ± 3	20%	16 ± 5	31%
8	(above 46)	35 ± 8	22%	34 ± 8	23%	14 ± 2	14%	16 ± 4	25%
40	(15–70)	34 ± 6	18%	34 ± 6	18%	14 ± 3	21%	15 ± 3	20%

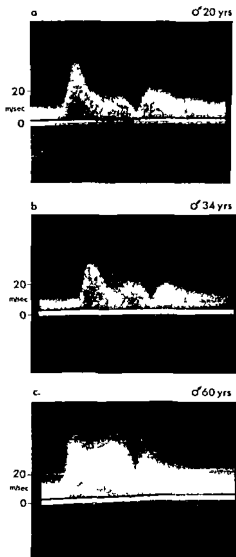


Fig 6
Velocity spectrum from the ophthalmic artery of normal subjects of different age a) male 20 years b) male 34 years c) male 60 years

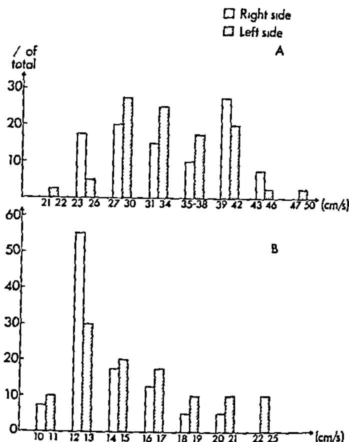


Fig 7

Distribution of the peak systolic velocities in A) ophthalmic artery B) lateral posterior ciliary arteries

Discussion

ing continuous wave ultrasound for measuring blood flow (Tokoro 1972 ...mamoto 1975) velocities in all vessels within the sound beam will be measured simultaneously Our measurements were performed with pulsed ultrasound giving range resolution and thus the possibility of interference from undersirable vessels will be minimal

In this study we have demonstrated that it is possible to measure blood flow velocities in defined parts of the ophthalmic arteries and in the posterior ciliary arteries reproducibly in normal persons

Table II

Mean sd and variation coefficient of ten measurements from the ophthalmic artery 8 mm below skin surface and from the lateral posterior ciliary arteries for three individuals

Subject (Age)	Mean sd and variation coefficient of the peak systolic velocities (cm/s)							
	Ophthalmic artery				Lateral posterior ciliary arteries			
	Right side		Left side		Right side		Left side	
J C (28)	37 ± 4	11%	33 ± 3	9	1? 8 ± 0 9	8?	13 1 ± 1 3	10%
S B (38)	4? ± 2	5%	40 ± 1	3 ?	13 1 ± 0 9	7	11 6 ± ? 2	15%
S K (3?)	31 ± 3	10%	33 ± 4	1? ?	12 9 ± 1 0	8	12 9 ± 1 4	11%

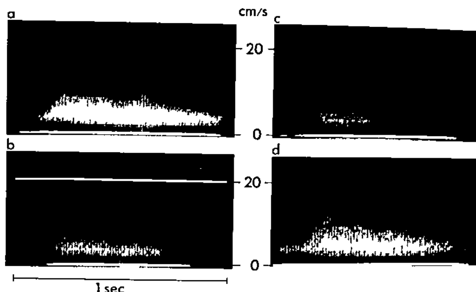


Fig 8

Velocity changes in the lateral posterior ciliary arteries following raised intraocular pressure achieved by placing different weights on the corneal surface for 30 seconds (Superimposion of about 10 cycles) a) Normal velocity spectrum b) 35 g c) 60 g d) after removing weights

The variation coefficients are rather great (20%) (Table I) and of the same order for the ophthalmic arteries as for the posterior ciliary arteries

Repeated measurements on the same person showed a variation coeffecient of about 10% (Table II) The difference between the variation coefficients of these two groups is probably explained by anatomical variations

The angle between the blood stream and the position of the sample volume can not be known for certainty The posterior ciliary arteries consist normally of two main bundles one on the temporal and one on the nasal side of the optic nerve (Hayreh & Dass 1962 Hayreh 1962) With our procedure the angle between the sound beam and the blood stream will be small (Fig 4) and thus the influence on the measured velocities minimal An angle of ± 15 for example would reduce the measured velocity only in the order of 3%

The course of the ophthalmic arteries shows greater variation Signal/noise ratio however is good and finding maximum signals corresponding to a minimum angle is easy

The sample area is given by the intensity of the sound which is proportional the field in the second power

The diameter of the effective sample area in our case will be less than 4 mm (F 2)

When measuring behind the eyeball with a cylindric sample volume with a length of 4 6 mm and a diameter of less than 4 mm the frequency spectrum of the backscattered sound will be a superimposition from several vessels We have assumed that the main contribution will be from the lateral posterior ciliary arteries Interference from other branches of the ophthalmic artery is possible As the blood flow in the central retinal artery is very small compared to that in the ciliary arteries (Alm & Bill 1973) this contribution is probably negligible Other branches of the ophthalmic artery will according to their anatomical course usually not interfere but may in case of vascular anomalies play a role

We have measured the flow velocities in the terminal trunk of the ophthalmic artery and in the lateral posterior ciliary arteries at different intraocular pressure This increase in pressure had no effect on the flow velocities in the ophthalmic artery Changes in the velocities in the lateral posterior ciliary arteries however were considerable (Fig 8) In particular the diastolic part of the cycle disappeared with only 35 g weight on the cornea

The form of the maximum velocity curve from the small arteries like the ophthalmic artery and even from the lateral posterior ciliary arteries has been well preserved compared to the common carotid artery (Fig 5)

The shape of the maximum velocity curve changed with increasing age showing a significant increase in the second systolic velocity peak in the older persons (Fig 6) This increase is probably due to structural changes in the vessel wall

With our instruments it is possible to measure velocities above 2 3 cm/s corresponding to the cut off frequency of the high pass filter which is necessary to remove noise from slowly moving targets

When using ultrasound doppler to measure blood flow velocities uninvasively one problem is to reproduce the position of the sample volume from one measurement to the other With knowledge about the topographical anatomy and an exactly known size of the sample volume as is the fact using pulsed ultrasound adequate reproducibility seems possible

When using ultrasound for measuring in the orbit the possibility of damaging effects in the eye must be considered So far no definite safety limits of ultrasound in ophthalmology have been determined Experiments with pulsed ultrasound in rabbits (Barnett & Kosoff 1977) using a 7 5 MHz focused transducer with a mean power output of 160 mW/cm² on retina and 20 mW/cm² on the cornea for 30 min showed no morphological changes

In this study the mean power into the eye was 28 mW/cm² Exposure time was kept as short as possible and did not exceed 15 min in any of the subjects No adverse effects were observed

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Acknowledgments

n to express their gratitude to Rune Aasl d M Sc. PhD Department of gy University of Trondheim for advice with the signal processing and M Sc Division op Physical Electronics Norwegian Insitute of Technology heim for assistance with the acoustic field measurements

References

Alm A & Bill A (1973) Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (macaca irus) a study with radioactively labeled microspheres including flow determinations in brain and some other tissues *Exp E e Re* 15 15–29

Angelsen B A J & Brubakk A O (1976) Transcutanous measurement of blood flow velocity in the human aorta *Cardiovascular Res. 10* 368–379

Barker D W (1970) Pulsed Ultrasonic Doppler Blood Flow Sensing IEEE Trans on Sonics and Ultrasonics Vol SU 17 No 3 170–185

Barnett S B & Kossoff G (1977) Negative Effects of Long Duration Pulsed Ultrasound on the Retina of Cats In White D (Ed) Ultrasound in Medicine Vol 3 pp 095 019 Plenum Press New York.

Brubakk A O Angelsen B A J & Hatle L (1977) Diagnosis of valvular heart disease using transcutaneous doppler ultrasound *Cardiovascular Res 11* 461–469

Engan H (1978) Measurements on Ultrasound Transducers Working note ELAB SINTEF Trondheim. Project No 480/2 05

Hayreh S S (1962) The ophthalmic artery III Branches. *Brit J Ophthal. 46* 912 947

Hayreh S. S. & Dass R. (1962) The ophthalmic artery II Intra-orbital course *Brit J Ophthal 46* 165 185

Hickam J B & Fraser R (1966) Studies of the retinal circulation in man. Observations on vessle diameter arteriovenous oxygen difference, and mean circulation time *Circulation* 22 09 316

Horven I Nornes H Sundalen P & Tonjum A. M. (1971) Dynamic tonometry in carotid occlusive disease. *Acta ophthal. (Kbh.) 49* 913–990

Kahle W Leonhardt H & Platzer W (19 6) Color Atlas and Textbook of Human Anatomy Vol. 1 325 Georg Thieme Verlag

Kossof G (1965) Balance technique for the measurement of very low ultrasonic power outputs. *A mer 35* 660–661

Matre K (1979) Measurements of Ultrasonic Power Working note, ELAB SINTEF Trondheim Project No 10

Niesel P & Gassmann H. B (1979) Direkte fluorometrische Untersuch augenhinter grund. *Ophthalm* 24 –

Tokuro T (197 Relationship between the and the intraocular pressure of rabbit eye. *Invest* 954

Yamamoto Y (197 Doppler examination *Eur* 5 32–

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The present material includes [illegible]

[illegible] patients with clinical [illegible] Both of the diseases are [illegible] generalized giant cell arteritis [illegible]

The frequency of giant cell arteritis [illegible] 1977) but awareness of the disease has [illegible] 1984) Classical hereditary studies are not [illegible] registered for the last 45 years. Further [illegible] age of 50 years Liang et al (19[illegible]) have [illegible] pairs of closely related patients suggested that [illegible] which predispose elderly individuals to [illegible] arteritis Up to the present it has been [illegible] connection between such factors and the HLA [illegible]

Table I

Frequency of phenotypes in patients and the control population Giant cell arteritis (N=88) Control (N=3164) *P* (Fisher)

HLA antigen	Number	%	Number	%	
A1	27	30.7	993	31.4	0.496
A2	49	55.7	1690	53.4	0.378
A3	27	30.7	870	27.5	0.291
A9	10	11.4	554	17.5	0.082
A10	11	12.5	285	9.0	0.172
A11	3	3.5	331	10.5	0.015
A28	6	6.8	278	8.8	0.340
Aw19	25	28.4	595	18.8	0.020
B5	12	13.6	342	10.8	0.245
B7	21	23.9	911	28.8	0.188
B8	28	31.8	731	23.1	0.041
B12	14	15.9	794	25.1	0.029
B13	5	5.7	133	4.2	0.317
B14	2	2.3	123	3.9	0.334
B18	6	6.8	234	7.4	0.523
B27	13	14.8	266	8.4	0.035
Bw15	13	14.8	566	17.9	0.2[illegible]6
Bw16	5	5.7	165	5.2	0.491
Bw17	5	5.7	259	8.2	0.268
Bw21	1	1.1	104	3.3	0.215
Bw22	2	2.3	111	3.5	0.403
Bw35	9	10.2	414	13.1	0.274
Bw40	24	27.3	579	18.3	0.027
			(N=1016)		
Cw1	3	3.5	49	4.8	0.392
Cw2	15	17.0	96	9.4	0.024
Cw3	33	37.5	346	34.1	0.293
Cw4	8	9.1	139	13.7	0.145

Results

Table I shows the results Five antigens (HLA Aw19 −B8 −B27 −Bw40 and −Cw2) showed increased values in the present patients ($0.05 > P > 0.01$) while two antigens showed decreased values (HLA A11 and −B12) If the *P* values are corrected by multiplication by the number of studied properties (27) then the differences are not significant

The first patient to be studied was one of a monozygotic pair of twins both of whom suffered from giant cell arteritis (Kemp 1977 the twins are only counted as one patient in the present material) Further two cases of familial occurrence of the disease complex were observed A 77 year-old woman included in the present material had a sister (deceased) who had developed severe temporal arteritis with bilateral loss of vision some seven years earlier One 70-year-old woman also included in the material had an older sister with polymyalgia rheumatica, but no histologically verified arteritis Information was obtained regarding the above relatives from the hospital to which they had been admitted

Discussion

HLA B8 has previously been demonstrated as occuring more frequently in patients with temporal arteritis and polymyalgia rheumatica The International HLA and Disease Registry in Copenhagen has incorporated the present data in a new combined analysis (1979) It was found that for HLA B8 in 222 patients with giant cell arteritis (the 9 patients of Terasaki et al are not included) there was a relative risk of the disease in the antigen bearers equalling 1.76 ($P = 0.003$) Svejgard & Ryder (1977) state however that the significance limit in connection with combined analyses should be as low as 0.0004 in order to avoid false associations Thus it is only an indication

The present material includes 19 patients with the clinical diagnosis of polymyalgia rheumatica. It was impossible to determine retrospectively how many of the patients with clinical temporal arteritis suffered initially from symptoms of polymyalgia Both of the diseases are in all probability cardinal manifestations of a generalized giant cell arteritis (Sørensen & Lorenzen 1977)

The frequency of giant cell arteritis in the Danish population is increasing (Kemp 1977) but awareness of the disease has also increased since 1934 (Horton et al 1934) Classical hereditary studies are not possible as the disease has only been registered for the last 4 years Further very few suffer from the disease before the age of 50 years Liang et al (1974) have in connection with their report of four pairs of closely related patients suggested that there are unknown genetic factors which pre pose elderly individuals to polymyalgia rheumatica and temporal arteritis U the present it has been impossible to demonstrate any definite connection b n such factors and the HLA system

Acknowledgment

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References

Bodmer W F (1972) Evolutionary significance of the HL A system *Nature 237* 139–145 & 183

Combined analysis from the HLA and Disease Registry Tissue Typing Laboratory University Hospital Copenhagen (1979) Unpublished data

Hazleman B Coldstone A & Voak D (1977) Association of polymyalgia rheumatica and giant cell arteritis with HLA B8 *Brit Med J 2* 989–991

Horton B T Magath T B & Brown G E (1934) Arteritis of the temporal vessels A previously undescribed form *Arch intern Med 53* 400–409

Hunder G G Sheps S G Allen G L & Joyce J W (1975) Daily and alternate-day corticosteroid regimes in treatment of giant cell arteritis *Ann Int Med 82* 613–618

Hunder G G Taswell H F Pineda A A & Elveback L R (1977) HLA antigens in patients with giant cell arteritis and polymyalgia rheumatica *J Rheum 4* 321–323

Hunder G G & Allen G L (1978) Giant cell arteritis Review *Bull rheum Dis 19* 980–986

Kemp A (1977) Monozygotic twins with temporal arteritis and ophthalmic arteritis Acta ophthal *(Kbh) 55* 183–190

Kissmeyer Nielsen F & Kjerbye K E (1967) Lymphocytotoxic microtechnique purification by flotation Report of a conference and workshop Torino and Saint Vincent Italy Munksgaard (Copenhagen) pp 381–383

Liang G C Simkin P A Hunder G G Wilske K R & Healey L A (1974) Familial aggregation of polymyalgia rheumatica and giant cell arteritis *Arthr Rheum 17* 19–24

Seignalet J Janbon C Sany J Janbon F Bidet J M Brunel M Jourdan J & Busiere J L (1977) HLA in temporal arteritis *Tissue Antigens 9* 69

Svejgaard A & Ryder L P (1977) Associations between HLA and disease In HLA and Disease Eds (J Dausset & A Svejgaard) Munksgaard (Copenhagen) 46–71

Sørensen S S & Lorenzen I (1977) Giant-cell arteritis temporal arteritis and polymyalgia rheumatica *Acta Med Scand 201* 207–213

Terasaki P I Healey L A & Wilske K R (1976) Distribution of HLA haplotypes in polymyalgia rheumatica *New Engl J Med 295* 905

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THE COLOUR OF THE OPTIC DISC VARIATION WITH LOCATION OF ILLUMINATION

BY

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The variation of the colour of the optic disc was examined with a slit lamp and contact lens in 200 normal subjects simply by moving the image of the slit across the optic disc This event was photographed in 15 subjects and colour densitometry was performed The temporal part of the pale central excavation changes colour to red when illuminated nasally and vice versa
The colour change could not be provoked in subjects with normal discs with flattening of the temporal disc sector The whole neurorim reddens the whole way round when the slit hits the optic disc border and dependent on fundus pigmentation slight redness was produced even when the slit was placed outside the disc in the neighbourhood of the border

Key words central excavation – colour change – microdensitometry – optic disc colour

The colour of the optic disc is still an important clinical landmark in ophthalmology since it is explicit correlated to the visual function (Cogan 1966 Walsh & Hoyt 1969) It is well known that the colour of the optic disc changes with the colour temperature of the light source (Miller & George 1978) and the age of the lens (Said & Weale 1959 Snydacker 1964) It is also known that colour changes with the incident angle from the light source Since the importance of this fact is only briefly mentioned in the literature (Kronfeldt 1967 Schwartz 1973) we have studied this phenomenon with the aid of a slit lamp and a contact lens simply by moving the image of the slit across the optic disc in 15 cases photographs of this procedure were analyzed in a densitometer

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Materials and Methods

200 normal subjects (age 6–87 mean 42 refractive error less than ± 3 diopters) had both of their optic discs examined in the Haag Streit or Rodenstock slit lamp employing a Goldmann fundus contact lens When the image of the slit was moved horizontally or vertically across the disc the colour (redness) of the illuminated area and of the rest of the disc was noted as well as the point at which the disc first begins to redden when the slit was moved towards and across the border

Fifteen cases with cup/disc ratio from 0 2 to 0 5 (estimated by colour contrast) were photographed (Zeiss photoslitlamp magnification × 2 Flash setting IV 350 Wsec slit 0 5 mm aperture 32 slit 3 Kodachrome 64) The transmission density of the diapositive was measured on the temporal slope of the optic disc excavation corresponding to an area with diameter 100 μ The density was read on a Reichert microdensitometer in the green (540 nm) and red (640 nm) locus where the luminousity is highest and where the unwanted absorption from overlapping between the colour forming pigments is lowest The density in the blue was not measured since it could be demonstrated in white areas only The differences between the densities at 640 nm and 540 nm is taken as an arbitrary index of the red colour The density at 640 nm denotes the colour hue and the density at 540 nm denotes the correction factor for variation in exposure

Thus linearity exists between density and the logarithm to the exposure in the proper exposure range of the film for both green and red and furthermore the characteristic curves for green and red have practically identical slopes Variations in exposure will therefore affect the densities in the same direction The linearity requirement is not totally fulfilled in the bright parts of the film a fact that is considered of minor importance

Results

Slit illumination of the optic disc results in a light spreading effect of the whole neurorim i e the peripheral part of the non excavated part of the optic disc This happens as soon as the slit image hits the optic disc border

In most subjects (92%) also the central physiological pallor turns red on the contralateral side of the optic cup Thus illumination nasally causes reddening temporally and vice versa. Most effective was disc illumination from the nasal side due to the larger area of the optic cup and perhaps due to a more bank like neurorim on the nasal side

In 6% of the subjects the excavation only glows when illuminated nasally but not temporally These subjects had temporal flat bright but normal optic discs with nasal displacement of the vessels

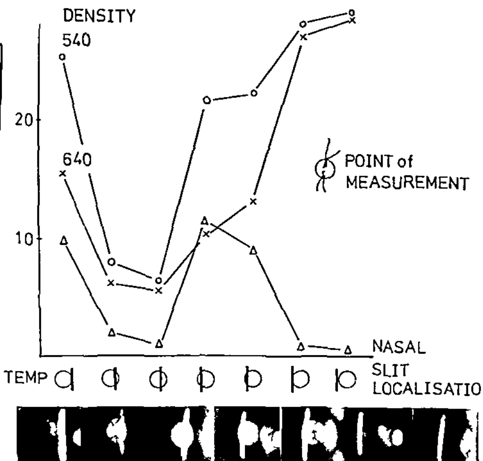


Fig 1

The redness of the central excavation as an illuminated slit moves stepwise across the left optic disc Black and white prints of the colour diapositives in which density measurements was made is seen below The red ×—× (640 nm) and green o—o (540 nm) density is given (arbitrary units) The difference Δ—Δ is an index of the redness

In all subjects the red glowing could also be provoked by moving the slit in the vertical direction

No difference between left and right eye could be demonstrated in any subject

In 35% of the subjects the optic disc begins to redden before the slit image reaches the border These subjects were predominantly blonds with sparse fundus pigmentation Thus 41% of the optic discs in blonds reacted in this way compared

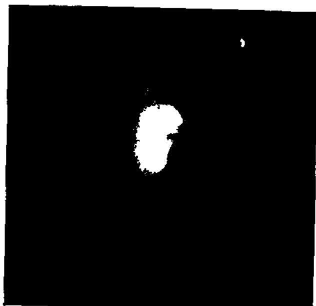


Fig 2
Slit lamp photo of the optic disc The central excavation is white at the temporal side but red at the nasal side



Fig 3
Slit lamp photo of the same optic disc The central excavation is now red temporally No light spreading outside the optic disc is seen

to 19% of the optic discs in dark haired However the reddening was always most *pronounced when the slit image reached the border of the neurorim*

Fig 1 demonstrates the colour change of the temporal part of the optic cup when the slit image si moved across the optic disc in a typical record of a subject with well developed optic cup The mean redness of the temporal excavation when the slit image is placed on the nasal neurorim is 0 96 (range 0 71 – 1 10 n = 15) The redness is given by the numerical difference between the densities of the film at 640 nm and 540 nm (arbitrary units)

From Fig 1 it is seen that the optic cup reddens with slit illumination both on the temporal border and also by nasal illumination

Fig 2 and 3 are *colour prints of diapositives of the colour change of the central* excavation when the slit image is placed temporally (Fig 2) and nasally (Fig 3) Light spreading in the retina is minimal compared to that of the optic disc

Discussion

This investigation has shown that the optic disc colour depends on the location of *the incident light on the disc* The demonstrated colour change of the physiological excavation of the disc from pale to red when the slit image is moved across the disc is puzzling Quigley & Anderson (1977) in a histopathological study on monkey eyes with descending optic atrophy considered the optic nerve fiber bundles and their adjacent glial columns as optic pathways According to them light is transfer red to the optic disc longitudinal to the nerveous fibres and adjacent glias cells and later diffused among the capillaries from which the reflected light takes its pink colour The contralateral reddening of the central excavation however is difficult to explain in this way On the other hand Gloster (1972 1973) in his study of optic *discs onto which* a grid shadow was projected through a fundus camera explains the light transfer of the optic disc tissue as an effect of a diffusing of light projected onto it

Still the nature of the colour change from pale to red of the contralateral part of the central excavation is obscure This phenomenon might be either a guidance or a reflection of red light originating from the vascular structures of the disc tissue Anothe possibility could be that the colour change is due to an unveiling of underly vascularity hitherto hidden by veiling reflections from tissue in front of it just a vascularity of the central excavation and apparently pale temporal parts of t disc is disclosed by fluorescein angiography (Hayreh 1969 1972)

When l hes a borderline surface two possibilities exist dependent on the angle of u Light can either be reflected or refracted Reflection can be

specular or scattered according to the properties of the surface In transparent media refractive index differences determine the degree of refraction Thus the redness of the optic disc must depend on whether light is scattered or reflected from the surface of penetrates the tissue until it is absorbed or finally reflected from the lamina cribrosa

The optical properties of the optic disc are not known in detail and need further investigations

The described dependence of optic disc colour on different location of the illumination of the disc has great clinical importance Schwartz (1973) advocates examination of the optic disc to be done with the aid of a contact lens and the slit lamp Par example with the direct ophthalmoscope the optic cup is estimated larger

Better understanding of the colour of the optic disc colour is achieved when considering the light reflected from the optic disc tissue as an information on what transformation the light undergoes when it strikes the optic disc texture

References

Cogan D G (1966) Neurology of the Visual System Springfield Ill Charles C Thomas Ibl
Gloster J (1973) Colorimetry of the optic disc *Trans Ophthal Soc U K 93* 242–249
Gloster J (1972) Concerning glaucomatous changes at the disc in Proc 2nd William Mackenzie Memorial Symp Glasgow 1971 Published in The Optic Nerve pp 298–303 J S Cant (Ed) H Kimpton Publishers London
Hayreh S S (1969) Blood supply to the optic nerve head and its role in optic atrophy glaucoma and oedema of the optic disc *Brit J Ophthal 53* 721–748
Hayreh S S (1972) Colour and flourescense of the optic disc *Ophthalmol gica 165* 100–108
Kronfeldt P C (1967) The optic nerve In Symp on Glaucoma Trans New Orleans Acad Ophthal pp 62–73 C V Mosby St Louis
Miller N R & George T W (1978) Monochromatic photography and ophthalmoscopy of the peripapllary retinal nerve fiber layer *Invest Ophthal 17* 1121–1124
Quigley H A & Anderson D R (1977) The histologic basis of optic disc pallor in experimental optic atrophy *Amer J Ophthal 83* 709–717
Said F S & Weale R A (1959) The variation with age of the spectral transmississivity of the living human crystalline lens *Gerontologica 3* 213–231
Schwartz B (1973) Cupping and pallor of the optic disc *Arch Ophthal (Chicago) 89* 2[illegible]
Snydacker D (1964) The normal optic disc Ophthalmoscopic and photographic studies. *Amer J Ophthal 58* 958–964
Walsh F B & Hoyt W F (1969) Clinical Neuro-Ophthalmology 3rd ed Williams & Wilkins Baltimore

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PULSED DOPPLER ULTRASOUND FOR MEASURING BLOOD FLOW VELOCITY IN THE HUMAN OPHTHALMIC CIRCULATION

BY

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This study was performed in order to develop a method for studying blood flow in the ophthalmic circulation Using a pulsed doppler system utilizing an ultrasonic frequency of 10 MHz blood flow velocities have been measured in the ophthalmic artery and in the arteries behind the eyeball (lateral posterior ciliary arteries) in 40 normal subjects The mean of the peak systolic velocities were 34 ± 6 cm/s in the ophthalmic artery and 14 ± 3 cm s in the lateral posterior ciliary arteries We conclude that blood flow velocities can be measured in defined vessel areas in the orbit

Key words ophthalmic artery – posterior ciliary arteries – blood flow velocities – pulsed doppler ultrasound

Using fluorescein photographic and photometric techniques blood flow in retinal arteries can be studied (Hickam & Frayser 1966 Niesel & Gassmann 1972)

Relative changes in blood flow to the eye in cases of carotid stenosis have been studied using ocular pulse amplitude (Hørven et al 1971) Only indirect measurement of blood flow can be performed in this way as changes in ocular volume and compliance will influence the result

Methods based on continuous wave ultrasound and the doppler principle have been prop › d for studying ocular blood flow (Tokoro 1972 Yamamoto 1975)

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These methods do not permit range resolution and therefore can not give a defined sample volume with respect to depth

The method presented in this paper has been based on pulsed doppler ultrasound which permits range resolution and hence measurement of blood flow velocities of selected depths Furthermore the size of the sample volume has been experimentally determined By this method it is possible to measure blood flow velocities more accurately in the ophthalmic and the posterior ciliary arteries

In this study the feasibility of the method has been demonstrated and the reproducibility of the measurements as well as the range of normal velocities have been documented

Methods

When ultrasound is transmitted into the body the soundwaves are scattered from inhomogenities in the tissue and in the blood The frequency shift (doppler shift f_d) in reflected waves is proportional to the velocity (v) of the scatterers according to the formula

$$f_d = 2 f_0 \frac{v}{c} \cos \Theta$$

where f_0 is the frequency of the transmitted soundwaves c is the sound velocity in the tissue and Θ is the angle between the soundbeam and the path of the scatterers

By pulsing the transmitted waves and detecting the backscattered soundwaves at a given time interval after transmission depth resolution is achieved (Baker 1970)

The ultrasonic doppler velocity meter used in this study has been described in detail (Angelsen & Brubakk 1976) and only its main features will be given here

The ultrasonic frequency is 10 MHz The repetition frequency was 19 5 kHz and a pulse length of 3 microseconds gives a sample length of 4 6 mm The ultrasonic transducer acts both as a transmitter and as a receiver The backscattered ultrasound is split into two channels by a quadrature demodulator in order to separate forward from backward flow

In order to remove signals from slowly moving tissues a high pass filter with a cut off frequency of 290 Hz was used The low pass filter has a cut off frequency of 9 3 kHz to remove high frequency noise

Using analogue estimators described earlier (Angelsen & Brubakk 1976 Brubakk et al 1977) the mean and maximum velocity in the sample volume can be displayed However due to the poor signal/noise ratio when measuring from the posterior ciliary arteries analogue estimation is difficult and the received signals were analyzed using a frequency analyzer This instrument is based on a z-chirp algorithm implemented by analogue shift registers (Reticon Corp Sunnywhale USA)

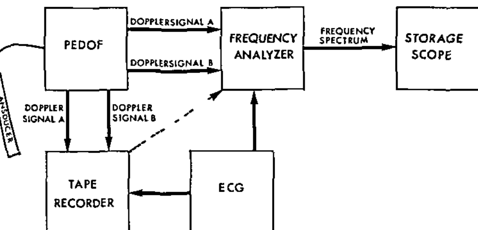


Fig 1

chematic view of the signal processing equipment PEDOF Pulsed Echo-Doppler Flow ieter is developed at the Division of Engineering Cybernetics University of Trondheim

n order to improve the time resolution of the received signals curves from about cardiac cycles were superimposed on an oscilloscope screen using the subject s ctrocardiogram as a trigger The maximum velocity has been given by the velope around the frequency spectrum

A schematic representation of the equipment used is shown in Fig 1

Initially we tested a transducer fastened inside a gonioscopic lens hoping that this uld facilitate aiming of the ultrasonic beam by simultaneous observation of the ina through a slit lamp However this was not the case firstly because of an avoidable pressure on the cornea secondly because of reduced mobility of the nsducer All measurements in this paper have therefore been done with a dshaped transducer made of lead zirconate titanate (Trade Mark PZT 5A ush Clevite) The transducer is quadratic (3 mm) and is backed by araldite The nsducer has an acoustic output power of 28 mW/cm² an efficiency of 12% a ase distortion of 2% and an impedance of 17Ω

The output power of the transducer was measured by transmitting the ultrasonic am into an absorber and detecting the ultrasonic energy by a sensitive balance ight (Mettler H L 52) The principle of this method had been described ewhere (Kosoff 1965 Matre 1979)

The acoustic field from the transducer was measured in water (Engan 1978) The eld was detected by another 10 MHz transducer having a small aperture (0 5 mm) front of it The rod transducer was scanned in the x-direction and in the

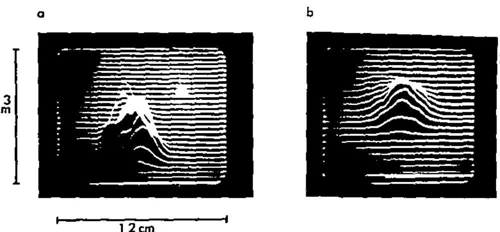


Fig 2

A three-dimensional representation of the ultrasonic field of the rodshaped transducer in water The field from the 10 MHz transducer is detected by scanning a 10 MHz rod transducer of same type with a 0 5 mm aperture in front in a plane 90 to the beam a) 1 cm from the crystal b) 3 cm from the crystal

supratrochlear artery

sample volume

nasal artery

ophthalmic terminal artery

nasal vein

Fig 3

End branches of the ophthalmic artery The orientation of the transducer and an estimation of the sample volume is shown about 8 mm below skin surface. Redrawn from W Kahle et al. (1978)

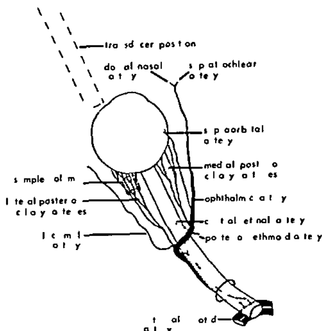


Fig 4

The most common pattern of some of the branches of the ophthalmic artery The sample volume is located lateral to the optic nerve 24 to 28 mm behind limbus cornea corresponding to the lateral main bundle of the posterior ciliary arteries The size of the volume is estimated to be 4 6 mm long and 4mm in diameter The direction of the transducer is indicated parallel to the optic nerve Redrawn after Hayreh S S (1976)

y-direction simultaneously Fig 2 shows a three-dimensional representation of the sound field in a plane 90 to the ultrasonic beam in water at two different depths

Blood flow velocity was measured in 40 subjects with no history of cardiovascular or eye diseases 16 women and 24 men (mean age 36 years range 15–70 years)

Nobody was using any drug at the time of the investigation The procedure was carefully explained to every subject and consent for doing the study was obtained All measurements were performed with the subjects in a supine position from the following sites Left and right ophthalmic artery and left and right arteries behind the eyeball (later called lateral posterior ciliary arteries)

In order to measure flow velocities in the ophthalmic artery the transducer was positioned on the nasal part of the closed upper eyelid Using methylcellulose as a coupling agent it is possible to measure without exerting any pressure on the tissue The transducer was moved until maximum velocity was obtained

The strongest signals were found at approximately 8 mm depth in all subjects Probably this will occur just before the division of the ophthalmic artery into the supratrochlear and the dorsal nasal artery (Hayreh S S 1962) The approximate location of the sample volume in relation to the vessels can be seen from Fig 3

In order to measure the velocities in the lateral posterior ciliary arteries eye movements must be eliminated therefore the subjects were asked to focus a black spot in the ceiling The cornea was anesthetized with oxybuprocain chloride 0 4% eye drops To avoid sound absorption in the cornea and in the lens the transducer was placed at the limbus cornea in a direction approximately parallel to the optic nerve axis (Fig 4) and the position was changed until the strongest signals were detected usually from a depth of 26 mm behind the corneal limbus

Adequate signals however could be detected at depths from 24 to 28 mm Using methylcellulose no pressure was needed to obtain acoustic contact with the eyeball

In order to demonstrate changes in flow following alteration of the intraocular pressure measurements were performed using different weights on the cornea (35–120 g)

Results

Typical velocity spectra from the common carotid artery the ophthalmic artery and the lateral posterior ciliary arteries are shown in Fig 5 Each spectrum is a superimposition of about 10 cardiac cycles from a normal subject 30 years of age

The peak systolic velocities found in the ophthalmic artery and the lateral posterior ciliary arteries in 40 normal subjects have been shown (Table I)

The mean of the peak systolic velocities have been grouped according to age No significant difference in maximum systolic velocities were found with increasing age The form of the maximum velocity curve however changed with increasing age (Fig 6)

In Fig 7 histograms of the peak systolic velocities have been shown The velocities ranged from 21 to 50 cm/s in the ophthalmic arteries and from 10 to 25 cm s for the lateral posterior ciliary arteries

In Table II the mean of the peak systolic velocities from each of 3 normal subjects measured 10 times weeks apart is presented

Fig 8 shows the effect on blood flow velocities in the lateral posterior ciliary arteries when intraocular pressure was changed The velocity spectrum in Fig 8a was recorded at normal intraocular pressure

In Fig 8b and 8c the intraocular pressure was increased for 30 seconds by placing an external weight 35 g and 60 g respectively on the cornea With increasing intraocular pressure the maximum flow velocities were reduced especially its diastolic part After release of the pressure (Fig 8d) the velocity spectrum was

slightly increased as compared to Fig 8a where normal flow conditions were to be expected Weights of 90 g and 120 g were also tried However no flow could be registrated in the posterior ciliary arteries

In the ophthalmic artery the change of intraocular pressure led to no measurable velocity changes

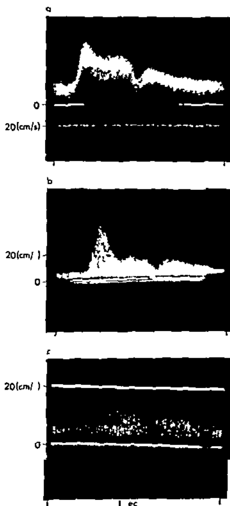


Fig 5

Velocity spe trum averaged over about 10 cardiac cycles for a) the commen carotid artery 13 mm below the skin surface b) the ophthalmic artery 8 mm below the skin surface c) lateral posterior ciliary arteries 26 mm behind limbus corneae

Table I

Mean SD and variation coefficient of the peak systolic velocities in the ophthalmic arteries 8 mm below skin surface and in the arteries 26 mm behind the corneal limbus (lateral posterior ciliary arteries) from 40 normal subjects grouped according to age

No	Age range	Mean SD and variation coefficient of the peak systolic velocities (cm/s)							
		Ophthalmic artery				Lateral posterior ciliary arteries			
		Right side		Left side		Right side		Left side	
9	(15–25)	36 ± 8	22%	33 ± 8	24%	16 ± 2	12%	15 ± 3	20%
8	(26–30)	34 ± 7	20%	34 ± 5	15%	13 ± 1	8%	13 ± 1	8%
8	(31–35)	32 ± 4	13%	33 ± 4	12%	14 ± 2	14%	14 ± 1	7%
7	(36–45)	37 ± 7	19%	36 ± 6	17%	14 ± 3	20%	16 ± 5	31%
8	(above 46)	35 ± 8	22%	34 ± 8	23%	14 ± 2	14%	16 ± 4	25%
40	(15–70)	34 ± 6	18%	34 ± 6	18%	14 ± 3	21%	15 ± 3	20%

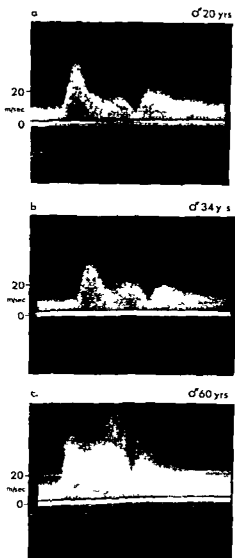


Fig 6

Velocity spectrum from the ophthalmic artery of normal subjects of different age a) male 20 years b) male 34 years c) male 60 years

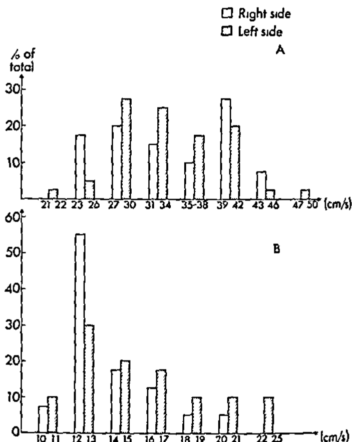


Fig 7

Distribution of the peak systolic velocities in A) ophthalmic artery B) lateral posterior ciliary arteries

Discussion

Using continuous wave ultrasound for measuring blood flow (Tokoro 1972 Yamamoto 1975) velocities in all vessels within the sound beam will be measured simultaneously Our measurements were performed with pulsed ultrasound giving range resolution and thus the possibility of interference from undersirable vessels will be minimal

In this study we have demonstrated that it is possible to measure blood flow velocities in defined parts of the ophthalmic arteries and in the posterior ciliary arteries reproducibly in normal persons

Table II

Mean, SD and variation coefficient of ten measurements from the ophthalmic artery 8 mm below skin surface and from the lateral posterior ciliary arteries for three individuals

Subject (Age)	Mean, SD and variation coefficient of the peak systolic velocities (cm/s)							
	Ophthalmic artery				Lateral posterior ciliary arteries			
	Right side		Left side		Right side		Left side	
JC (28)	37 ± 4	11%	33 ± 3	9%	12.8 ± 0.9	8%	13.1 ± 1.3	10%
SB (38)	4[illegible] ± 2	5%	40 ± 1	3%	13.1 ± 0.9	7%	1[illegible].6 ± 2.[illegible]	15%
SK (3[illegible])	31 ± 3	10%	33 ± 1	12%	12.[illegible] ± 1.0	8%	1[illegible].9 ± 1.1	11%

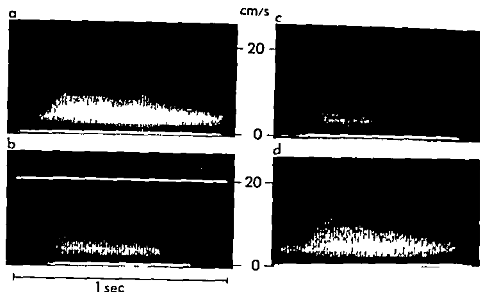


Fig 8

Velocity changes in the lateral posterior ciliary arteries following raised intraocular pressure achieved by placing different weights on the corneal surface for 30 seconds (Superimposion of about 10 cycles) a) Normal velocity spectrum b) 35 g c) 60 g d) after removing weights

The variation coefficients are rather great (20%) (Table I) and of the same order for the ophthalmic arteries as for the posterior ciliary arteries

Repeated measurements on the same person showed a variation coeffecient of about 10% (Table II) The difference between the variation coefficients of these two groups is probably explained by anatomical variations

The angle between the blood stream and the position of the sample volume can not be known for certainty The posterior ciliary arteries consist normally of two main bundles one on the temporal and one on the nasal side of the optic nerve (Hayreh & Dass 1962 Hayreh 1962) With our procedure the angle between the sound beam and the blood stream will be small (Fig 4) and thus the influence on the measured velocities minimal An angle of ± 15 for example would reduce the measured velocity only in the order of 3%

The course of the ophthalmic arteries shows greater variation Signal noise ratio however is good and finding maximum signals corresponding to a minimum angle is easy

The sample area is given by the intensity of the sound which is proportional to the field in the second power

The diameter of the effective sample area in our case will be less than 1 mm (Fig 2)

When measuring behind the eyeball with a cylindric sample volume with a length of 4 6 mm and a diameter of less than 4 mm the frequency spectrum t the backscattered sound will be a superimposition from several vessels We have assumed that the main contribution will be from the lateral posterior ciliary arteries Interference from other branches of the ophthalmic artery is possible A the blood flow in the central retinal artery is very small compared to that in the ci r arteries (Alm & Bill 1973) this contribution is probably negligible Other bran hes f the ophthalmic artery will according to their anatomical course u ally not nterfer but may in case of vascular anomalies play a role

We have measured the flow velocities in the terminal trunk of the ophtha artery and in the lateral posterior ciliary arteries at different intr lar press This increase in pressure had no effect on the flow velocities in the op at artery Changes in the velocities in the lateral posterior ciliary arteries were considerable (Fig 8) In particular the diastolic part of the cle disappeared with only 35 g weight on the cornea

The form of the maximum velocity curve from the small arteries l k the ophthalmic artery and even from the lateral posterior ciliary arteries has been well preserved compared to the common carotid artery (Fig 5)

The shape of the maximum velocity curve changed with increasing age showing a significant increase in the second systolic velocity peak in the older persons (Fig 6) This increase is probably due to structural changes in the vessel wall

With our instruments it is possible to measure velocities above 2 3 cm s corresponding to the cut off frequency of the high pass filter which is necessary to remove noise from slowly moving targets

When using ultrasound doppler to measure blood flow velocities uninvasively one problem is to reproduce the position of the sample volume from one measurement to the other With knowledge about the topographical anatomy and an exactly known size of the sample volume as is the fact using pulsed ultrasound adequate reproducibility seems possible

When using ultrasound for measuring in the orbit the possibility of damaging effects in the eye must be considered So far no definite safety limits of ultrasound in ophthalmology have been determined Experiments with pulsed ultrasound in rabbits (Barnett & Kosoff 1977) using a 7 5 MHz focused transducer with a mean power output of 160 mW cm^2 on retina and 20 mW/cm^2 on the cornea for 30 min showed no morphological changes

In this study the mean power into the eye was 28 mW/cm^2 Exposure time was kept as short as possible and did not exceed 15 min in any of the subjects No adverse effects were observed

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References

Alm A & Bill A (1973) Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (macaca irus) a study with radioactively labelled microspheres including flow determinations in brain and some other tissues *Exp Eye Res 15* 15–29

Angelsen B A J & Brubakk A O (1976) Transcutanous measurement of blood flow velocity in the human aorta *Cardiovascular Res 10* 368–379

Barker D W (1970) Pulsed Ultrasonic Doppler Blood Flow Sensing IEEE Trans on Sonics and Ultrasonics Vol SU 17 No 3 170–185

Barnett S B & Kossoff C (1977) Negative Effects of Long Duration Pulsed Ultrasound on the Retina of Cats In White D (Ed) Ultrasound in Medicine Vol 3 pp 2035–2039 Plenum Press New York

Brubakk A O Angelsen B A J & Hatle L (1977) Diagnosis of valvular heart disease using transcutaneous doppler ultrasound *Cardiovascular Res 11* 461–469

Engan H (1978) Measurements on Ultrasound Transducers Working note EI AB SINTEF Trondheim Project No 48072705

Hayreh S S (1962) The ophthalmic artery III Branches *Brit J Ophthal 46* 212–247

Hayreh S S & Dass R (1962) The ophthalmic artery II Intra-orbital course *Brit J Ophthal 46* 165–185

Hickam J B & Frayser R (1966) Studies of the retinal circulation in man Observations on vessle diameter arteriovenous oxygen difference and mean circulation time *Circulation 33* 302–316

Hørven I Nornes H Syrdalen P & Tønjum A M (1971) Dynamic tonometry in carotid occlusive disease *Acta ophthal (Kbh) 49* 913–920

Kahle W Leonhardt H & Platzer V V (1978) Color Atlas and Textbook of Human Anatomy Vol 1 325 Georg Thieme Verlag

Kossof G (1965) Balance technique for the measurement of very low ultrasonic power outputs *Acoust Soc Amer 38* 880–881

Matre K (1979) Measurements of Ultrasonic Power Working note EI AB SINTEF Trondheim Project No 180777 10

Niesel P & Cassmann H B (1972) Direkte fluorometrische Untersuchung am augenhinter grund *Ophthalmologica 165* 297–302

Tokoro T (1972) Relationship between the blood flow velocity in the ciliary body and the intraocular pressure of rabbit eye *Invest Ophthal 11* 915–924

Yamamoto Y (1975) Doppler examination of blood flow in the ocular fundus *Bill Ophthal (Basel) 93* 32–40

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abbreviations and symbols only standardized terms should be used

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Examples of references

Davanger M (1980) Pseudo-exfoliation material Acta Ophthalmol (Kbh) 58 512–519

Savino P J Glaser J S & Rosenberg M A (1979) A clinical analysis of pseudopapilledema II Visual field defects Arch Ophthalmol 97 71–75

Sorensen G D & Barr W A (1968) Murino amyloid deposits and cellular relationships In Mandema E, Ruinen L, Scholten J H & Cohen A S (eds) Amyloidosis p 59 Exerpta Medica Amsterdam

Vogt A (19 9) Textbook and Atlas of Slit Lamp Microscopy of the Living Eye Vol II Lens and Zonule p 422 Verlag Wavenborgh Bonn.

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